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NITROGEN METABOLISM DURING PREGNANCY.

By Karl M. Wilson, M. D.

(From the Obstetrical Clinic, Johns Hopkins Hospital.)

During the past 25 years a number of observers have made contributions to our knowledge of some of the problems of metabolism arising in the course of a normal pregnancy, labor and the puerperium. Unfortunately, practically all of the observations upon women have been made on patients studied only for the last few weeks of the pregnancy, and in some cases only for the last few days, whereas the study of the various phases of metabolism in the early months of pregnancy has been almost wholly neglected.

Various observers have approached the subject through the study of the metabolic processes in pregnant animals. On account of the shorter duration of the pregnancy, together with the possibility of keeping the animal on a fixed diet throughout the entire period of the pregnancy, such studies are naturally more satisfactory than is the case when pregnant women are studied.

Hageman, Jägeroos, Ver Eecke and Bar have made extensive studies on the nitrogen metabolism of pregnant animals throughout the entire duration of their pregnancies. Ver Eecke used pregnant rabbits; Hageman and Jägeroos carried out their observations on pregnant dogs (the duration of the pregnancy being 60 days), whereas Bar used both rabbits and dogs, the latter proving to be much more satisfactory for purposes of study.

Hageman found that in the dog the pregnancy could be divided into two distinct metabolic periods, corresponding in time to the two halves of the pregnancy. In the first, the animal was found to be in a state of negative nitrogen balance, storage of nitrogen beginning with the middle of pregnancy and continuing up to the time of labor, this capacity for storage becoming more marked as the pregnancy advanced, according as the needs of the developing ova became greater.

Jägeroos obtained similar results in his experiments but concluded, after calculating the nitrogen content of the embryos and their appendages, that, taking the time of the pregnancy as a whole, it is to be regarded as a period of sacrifice on the part of the mother.

Ver Eecke, after extensive studies on pregnant rabbits, also concludes that the period of pregnancy is to be regarded as a period of sacrifice by the mother, or, as he expresses it, "a sacrifice on the part of the individual for the sake of the species."

Bar, whose experiments were carried out under more nearly ideal conditions than those of the above-mentioned observers, also recognized two distinct periods in the nutrition of the pregnant animal, corresponding in time to the two halves of the pregnancy; but his findings differ in certain respects from those of Hageman and Jägeroos. In common with them, he

found the second half of the pregnancy to be characterized by a marked and progressive storage of nitrogen up to the time of labor. In the first half of the pregnancy, however, he distinguished two periods; first, a period extending from the beginning of the pregnancy to the second or third week, during which there was a storage of nitrogen, this being followed by what he describes as the period of "saturation," in which the retention of nitrogen is less marked or entirely absent, the animal being either in a state of nitrogen equilibrium or even showing a negative balance. This period continued up to the middle of pregnancy and was believed to be due to an increase in the disassimilation processes. In observations made on two pregnant rabbits he found a storage of nitrogen throughout the whole period of pregnancy. Others were studied, but the results were unsatisfactory.

From the whole series of observations made on pregnant animals, he concluded that in the normal, healthy animal, living under proper hygienic and dietary conditions, and going through a normal pregnancy, the period of gestation is not to be regarded as a period of sacrifice on the part of the mother, but may actually be a period of gain, with an increase in her nitrogen capital.

Murlin, studying pregnant dogs, found a loss of nitrogen throughout the first four weeks of the pregnancy, followed by a marked storage in the second half. One of his animals showed a net gain of 8.69 gm. of nitrogen, while another showed a net loss of 55.6 gm. of nitrogen from the mother's body.

All the observations made on the nitrogen metabolism of pregnant women go to show that, in the second half of the pregnancy, we have a period corresponding to the same period observed in pregnant animals, characterized by the marked ability of the organism to store nitrogen. Beginning with Zacharjewsky, this subject has been more or less extensively studied by Schrader, Sillevis, Slemons, Hahl and Bar. Slemons found this capacity for storage to be more marked in multiparæ, whereas Hahl and Bar found it to be greater in primiparous women.

Up to the present time, no one has made any extensive observations on the nitrogen exchange in the early months of a human pregnancy, and it has been more or less assumed that, inasmuch as the needs of the growing ovum are infinitesimal at this stage, there is either no change at all in the general nitrogen metabolism, or that we have a period of loss, as seen in the first half of pregnancy in dogs, and development of the ovum at the expense of the maternal organism.

The earliest extensive observations are those reported by Hoffström, who in a single patient made a very careful study of the nitrogen, sulphur, phosphorus, calcium and magnesium exchange during the last 24 weeks of pregnancy. In this case, personal weekly analyses of the foodstuffs used, and of the urine and feces, were also made.

In regard to the nitrogen metabolism, he found that nitrogen storage occurred throughout the whole period of study. This averaged 1.84 gm. per day, so that the total retention amounted to 310 gm. Of this nitrogen retained, he estimates that 101 gm. were devoted to the development of the ovum, while the balance of 209 gm. was added to the maternal organism. Of these 209 gm., he estimates that 51 gm. were utilized in the growth and development of the breasts leaving a balance of 158 gm. of "Restmaterial," forming a maternal reserve. He is unable, however, to state the exact form which this reserve takes or the manner in which it is utilized by the organism.

From the study of this patient he draws the following general conclusion: "Normal pregnancy in a healthy maternal organism, living under normal exterior conditions, produces a marked retention of nutritive materials, which suffices for the development of the product of conception and its adnexa, for the modification of the generative organs, and the formation of a reserve fund which will be utilized during labor and the puerperium. Normal pregnancy does not then constitute for the mother a period of loss, nor yet is it for her a period of gain."

During the last two years, we have had the opportunity to make observations on the nitrogen metabolism in three normal pregnancies: in one patient for a period of four weeks, from the tenth to the fourteenth weeks of the pregnancy. The other two patients were studied for the last 133 and 101 days of their respective pregnancies and also for a short time in the puerperal period.

Method of Study.

The methods adopted in the study of these patients are quite similar to those used by Slemons in the cases studied by him in this clinic and reported in 1904. A fairly liberal diet was allowed, both in quantity and character of foodstuffs used. This was particularly true in the first woman, who was a private patient of Dr. Williams, and she was allowed a very wide selection in the choice of her diet. In all instances the patients were allowed sufficient food to satisfy the appetite, but were not compelled to eat all the food allotted for a given meal when they did not desire it. Each article of food was especially prepared for the individual patient, and was carefully weighed or measured before being given to her. The residue, if any, was collected and again weighed or measured. The nitrogen content of the food ingested was computed partly from the tables of Atwater and Bryant and partly from personal analyses. At all times the patients were kept under as normal external conditions as was possible, particularly in regard to exercise, and were not allowed to lead too sedentary a life.

The urine was collected for 24-hour periods, and carefully preserved; of these specimens daily analyses were made. From these daily analyses the daily average nitrogen content of the urine, for periods of a week at a time was estimated. Daily determinations of the ammonia nitrogen were made on all specimens and the amino-acid nitrogen was also estimated for variable periods. The total nitrogen was determined by the Kjeldahl method, the ammonia by the method of Folin and the amino-nitrogen by the Van Slyke method. All determinations were made in duplicate. The feces were preserved and analyzed weekly, and from the results obtained, the average daily nitrogen content was calculated. The patients were weighed at frequent intervals.

STUDY OF CASES.

CASE I.—M. V. W., white, age 28 years. Admitted May 30, 1914. The past history was unimportant.

The present pregnancy is her first, and has been uneventful, except for the fact that the first specimen of urine examined showed the presence of a faint trace of albumin (not in sufficient quantity to give a reading in the Esbach tube). This proved to be a transient phenomenon. Her last menstrual period began on March 7, 1915, and was perfectly normal, lasting for five days. The patient has had no subjective symptoms of any kind since the pregnancy began.

TABLE I, CASE I.

DAILY AVERAGE NITROGEN EXCHANGE.

Week.	Daily N. Intake.	N. Output. Urine.	N. Output. Feces.	Total.	Balance.	Weekly Storage.	Total Storage.	Calories.	Weight. Lbs.
I	13.04	8.10	0.70	8.80	+4.24	29.68	29.68	2499	132¾
II	10.78	8.06	0.69	8.75	+2.03	14.21	43.89	1973	132¾
III ...	10.73	8.22	0.73	8.95	+1.78	12.46	56.35	2081	134¼
IV ...	7.88	6.73	0.63	7.36	+0.52	3.64	59.99	1705	130¼

The physical examination showed the patient to be a well developed, well nourished woman, in whom no physical abnormalities were detected. The blood pressure was 120 mm. The weight at the beginning of observations was 128½ pounds.

Studies in metabolism were begun on June 2, 1915, and were continued for a period of four weeks. At the time this study was begun, the patient had missed two menstrual periods and was apparently between nine and ten weeks pregnant.

TABLE II, CASE I.

DAILY NITROGEN EXCHANGE. AMMONIA AND AMINO-NITROGEN OF UEINE.

Date.	Volume of Urine.	N. Intake.	N. Urine.	N. Feces.	N. Balance.	% of Ammon. N.	% of Amino-N.	Calories.	Weight. Lbs.
June 2....	915	12.59	7.20	0.71	+4.58	2.8	..	2273	128½
" 3....	1560	13.30	9.72	0.71	+2.87	3.8	3.2	2578	..
" 4....	1000	14.12	4.90	0.71	+8.52	7.1	3.1	2560	130½
" 5....	1830	12.87	9.48	0.71	+2.67	5.4	3.6	2251	..
" 6....	1500	12.86	7.86	0.71	+4.29	3.7	3.8	2572	131¾
" 7....	2120	13.28	9.94	0.71	+2.63	4.4	3.8	2739	..
" 8....	1660	12.29	7.55	0.68	+4.06	4.0	3.1	2524	132¾
" 9....	1750	11.88	8.09	0.68	+3.11	3.9	4.3	2150	..
" 10....	2030	13.57	9.36	0.68	+3.53	3.9	3.6	2419	133
" 11....	1660	12.28	7.44	0.68	+4.16	4.0	..	2203	..
" 12....	1360	12.82	7.62	0.68	+4.52	4.7	2.8	2360	132½
" 13....	1140	3.70	7.74	0.68	−4.71	3.5	..	647	..
" 14....	1230	10.17	8.44	0.68	+1.05	4.2	2.1	1832	131¾
" 15....	1460	11.04	7.78	0.75	+2.51	4.7	2.4	2202	..
" 16....	1375	10.60	8.00	0.75	+1.85	4.9	3.1	1992	132¾
" 17....	1620	10.99	8.39	0.75	+1.85	8.1	2.4	2108	..
" 18....	1910	10.25	7.48	0.75	+2.02	6.0	2.5	2062	133¾
" 19....	1570	11.87	7.94	0.75	+3.18	2.9	3.6	2323	..
" 20....	1830	10.01	9.09	0.75	+0.17	3.9	2.6	1961	133½
" 21....	1170	11.01	7.78	0.75	+2.48	3.7	2.7	2196	..
" 22....	1420	10.39	8.85	0.63	+0.01	6.0	2.3	1926	134¼
" 23....	1620	9.32	8.85	0.63	−0.16	5.1	2.1	1888	..
" 24....	960	7.94	6.59	0.63	+0.72	4.6	3.2	1615	132
" 25....	1100	9.30	6.62	0.63	+2.05	8.6	2.4	1875	..
" 26....	860	6.89	5.60	0.63	+0.66	4.8	3.6	1540	132½
" 27....	910	7.43	6.11	0.63	+0.69	5.4	2.0	1629	..
" 28....	900	7.43	7.37	0.63	−0.57	4.7	..	1855	130¾
" 29....	820	6.88	5.97	0.65	+0.26	5.7	3.2	1532	..
" 30....	750	7.46	4.99	0.65	+1.82	4.7	..	1534	130¼

In the study of the daily nitrogen exchange in this patient it was found, as is shown in the tables which follow, that she stored nitrogen from the time of the beginning of the observations and, with the exception of three isolated days, a plus balance was noted on every day during the period of study. On one of the days when a negative balance was noted, the patient had a gastric disturbance, was nauseated and ingested almost no food, the nitrogen balance on this occasion being −4.71 gm. On the other two occasions, both in the last week of study, the negative balance was very slight, being −.16 and −.57 gm. respectively. On only the one day during the period of study was there any gastric disturbance present, a point which I wish to emphasize.

In Table I, I have tabulated the actual daily average nitrogen exchange for the four weeks during which the study lasted.

Inasmuch as this patient was only observed for a period of four weeks, it seems that it might be advisable to tabulate the actual daily results obtained for comparison with the preceding. Table II shows the actual daily nitrogen exchange during the period of study, together with the ammonia and free amino-nitrogen of the urine for the corresponding days.

CASE II.—J. R., colored, age 19 years. Admitted February 5, 1914.

The past history was unimportant.

The present pregnancy is her first, and has been perfectly normal. The patient has had no nausea or vomiting at any time. Her last menstrual period began on November 15th, and was normal. Fœtal movements were first noticed about March 14th.

The physical examination showed no abnormalities.

A study of her metabolism was begun on March 4th, and was continued without interruption throughout the remainder of the pregnancy and for the first week after labor. Her weight at the time the observations were begun was 113 pounds. The following table shows the average daily nitrogen exchange for each week of the study up to the time of labor. (As will be explained later, this patient was delivered about four weeks prematurely, in the 36th week of her pregnancy.) Frequent routine examinations of the urine failed to reveal the presence of albumin, sugar or casts.

TABLE III, CASE II.

DAILY AVERAGE NITROGEN EXCHANGE.

Week of Preg.	N. Intake.	N. Output. Urine.	N. Output. Feces.	Total.	N. Balance.	Weekly Storage.	Total Storage.	Calories.	Weight. Lbs.
18	10.91	9.46	.54	10.0	+0.91	6.37	6.37	1740	112
19	10.10	6.40	.36	6.76	+3.34	23.38	29.75	1673	112½
20	12.07	8.54	.63	9.17	+2.90	20.30	50.05	1930	113
21	11.80	7.34	.64	7.98	+3.82	26.74	76.79	1930	114
22	11.70	8.88	.67	9.55	+2.15	15.05	91.84	1955	114½
23	12.50	9.61	.55	10.16	+2.34	16.38	108.22	2023	..
24	12.15	9.15	.44	9.59	+2.56	17.92	126.14	1916	116
25	12.30	8.49	.54	8.94	+3.36	23.52	159.66	2012	117¼
26	11.87	9.68	.56	9.64	+2.23	15.61	175.27	1986	117¼
27	11.72	9.47	.52	9.99	+1.73	12.11	187.38	2153	117½
28	11.76	6.25	.31	6.56	+5.20	36.40	223.78	2042	118¾
29	11.36	8.20	.28	8.48	+2.88	20.16	243.94	1874	119½
30	10.40	7.77	.36	8.13	+2.27	15.89	259.83	1722	120¼
31	10.90	7.60	.46	8.06	+2.84	19.88	279.71	1672	121
32	11.95	8.30	.40	8.70	+3.25	22.75	302.46	1762	122¼
33	12.21	7.77	.32	8.09	+4.12	28.84	331.30	1972	123½
34	11.62	6.09	.37	6.46	+5.16	30.96	362.26	1959	..
35	11.63	7.09	.40	7.49	+4.14	28.98	391.24	2150	125¾
36, 6 days	11.80	6.63	.48	7.11	+4.69	28.14	419.38	1683	126½
Day Deliv.	1.20	5.96	.63	6.59	..	..	..	..	..

Labor pains began at 10.00 p. m., July 14th, and after an uneventful labor lasting ten and one-half hours, the child was born at 8.30 a. m., July 15th. (Judging from the menstrual history given by this patient, the time when fœtal movements first became evident, and the size of the child, which was somewhat under the average, it seems evident that labor occurred between four and five weeks before full-term, apparently in the 36th week of pregnancy; and I have made calculations on that basis.)

The child weighed 2850 gm. The placenta and membranes weighed 540 gm.; the amount of blood lost was 375 gm. The weight of patient before delivery was 126½ pounds. The weight of patient immediately after delivery was 117 pounds, a net loss of nine and one-half pounds. Observations were continued on the patient for the first ten days of the puerperium and the following results were obtained:

The nitrogen intake averaged 11.34 gm. N. per day.

The nitrogen output:

Urine averaged	10.91 gm.	per day
Feces averaged	.82 gm.	"
Lochia averaged	.49 gm.	"
Milk averaged	.70 gm.	"
Total output	12.92 gm. N. per day.	

She thus showed a negative nitrogen balance during this period which averaged — 1.58 gm. N. per day. The weight of the patient at the end of the first ten days after labor was 112 pounds, and four days later this had still further decreased to 109 pounds.

CASE III.—E. Z., white, age 18 years. Admitted January 25, 1915. The past history was unimportant.

The present pregnancy is her first and has been normal in every respect up to the time of her admission to the hospital. There has been no nausea, vomiting, or other gastro-intestinal disturbances. Her last menstrual period occurred in the latter part of August, 1914. Fœtal movements were first noticed early in January, 1915.

The general physical examination showed a healthy woman in whom no abnormalities could be detected. The fundus of the uterus was two fingerbreadths below the level of the umbilicus. Active fœtal movements were readily appreciated, and the fœtal heart-sounds distinctly heard.

Observations on this patient were begun on January 27th and were continued without interruption throughout the remainder of pregnancy and for the first week of the puerperium. Her weight at the time the study was begun was 115 pounds. Frequent routine examinations of the urine throughout the period of study failed to show the presence of sugar, albumin or casts at any time.

From the history of the patient, and the findings at examination, it seems fair to conclude that this woman was apparently in about the 23d or 24th week of her pregnancy and was delivered about two weeks before the expected date of confinement, in the 38th week of the pregnancy.

In the following table is tabulated the average daily nitrogen exchange, together with the average and total storage according to the same scheme as that employed in the preceding case.

TABLE IV, CASE III.

DAILY AVERAGE NITROGEN EXCHANGE.

Week of Preg.	N. Intake.	N. Output.			N. Balance.	Weekly Storage.	Total Storage.	Calories.	Weight. Lbs.
		Urine.	Feces.	Total.					
24	15.33	11.31	0.86	12.17	+3.16	22.12	22.12	2310	116½
25	15.65	12.90	1.17	14.07	+1.58	11.06	33.18	2321	115¾
26	15.90	11.60	0.80	12.40	+3.50	24.50	57.68	2418	120½
27	15.83	13.13	1.60	14.19	+1.64	11.48	69.16	2365	119½
28	15.54	12.41	1.34	13.75	+1.79	12.53	81.69	2308	121¼
29	15.87	13.70	1.71	15.41	+0.46	3.22	84.91	2395	122½
30	16.28	13.39	1.39	14.78	+1.50	10.50	95.41	2416	123
31	16.39	13.77	1.40	14.81	+1.58	11.06	106.47	2448	123¾
32	16.09	14.20	1.27	15.47	+1.52	10.64	117.11	2522	125
33	18.50	14.06	0.88	14.94	+3.56	24.92	142.03	2765	127
34	19.72	12.78	0.66	13.44	+6.28	43.96	185.99	2988	129
35	19.57	12.58	0.82	13.40	+6.17	43.19	229.18	2945	129¾
36	19.62	12.08	1.17	13.25	+6.37	44.59	273.77	2981	131½
37	19.37	12.42	1.11	13.53	+6.04	42.28	316.05	3028	134
38, 3 days	19.84	12.07	1.05	13.12	+6.72	20.16	336.21	3003	133¼
Day Deliv.	7.76	11.21	1.05	12.26	..	..	..	..	..

Labor pains began at 1.00 a. m., on May 8, 1915, the entire labor being uneventful and ending spontaneously after a duration of 15 hours.

The child weighed 2960 gm. The placenta and membranes 480 gm. The amount of blood lost was 150 gm. The weight of patient before delivery was 133¼ pounds. The weight of patient immediately after delivery was 121¼ pounds, a net loss of 12 pounds.

The puerperium was perfectly normal, and the nitrogen exchange during the first week after labor was found to be as follows:

The nitrogen intake averaged 18.03 gm. N. per day.

The nitrogen output:

The urine averaged	15.96 gm.	N. per day
The feces averaged	1.06 "	"
The lochia averaged	3.40 "	"
The milk averaged	0.32 gm.	"
Total output	20.74 gm. N. per day.	

Thus, there was a negative nitrogen balance, which averaged — 2.71 gm. of nitrogen per day.

The weight of the patient at the end of the first week after labor was 117¼ pounds, and on May 23d, fifteen days after delivery, this had decreased still further to 115 pounds.

DISCUSSION OF RESULTS.

In considering these observations, one point to be emphasized is the fact that all three were made upon perfectly healthy women presenting perfectly normal pregnancies, and that none of them suffered from nausea, vomiting, or any of the other gastro-intestinal disturbances so frequently noted in early pregnancy. Indeed, inasmuch as it has been our experience that at least half of our patients go through the entire period of pregnancy without any of these disagreeable symptoms, the question arises as to whether the women suffering from such disturbances are to be regarded as being perfectly normal.

Case I, so far as I am aware, is the earliest pregnancy on which metabolism studies have been carried out for any extended period of time. In this patient storage of nitrogen was found to be taking place from the time the observations were begun until their close, and in the actual daily exchange a positive balance was noted on every day except three. The total storage of nitrogen during the period of observation amounted to 59.99 gm. N.

The period of observation in this patient probably extended from the tenth to the fourteenth weeks of her pregnancy at the latest, and it may have been begun slightly earlier. At this period of pregnancy the daily need of the developing ovum for nitrogen can be regarded as infinitesimal. Indeed, the total nitrogen content of the entire ovum probably does not exceed two or three grams, whence we may conclude that most of the nitrogen stored must have been added to the general maternal organism in some form, possibly to be drawn on later by the developing ovum when its needs became greater. In regard to the place of storage and the form assumed by this nitrogen, it is of course quite impossible to make any positive statement; although we must bear in mind that even at this early stage a portion of it is probably utilized in the growth and hypertrophy of the uterus and breasts.

Storage was found to be most active during the first three weeks of the study and was accompanied by an increase in the body weight of 1½ pounds. In the fourth week the conditions were quite changed, inasmuch as the average daily intake now fell to 7.88 gm. N. per day, and with this marked diminu-

tion in the intake (the caloric value of the diet at this time was not sufficient for a patient of her body weight) the patient lost four pounds in weight, as compared with the weight at the end of the preceding week. How is this to be explained?

One explanation might be in the possibility that she may have reached what Bar describes as the "period of saturation," in which disassimilation processes predominate. It is to be noted, however, that this marked change was not accompanied by any gastro-intestinal disturbances. Consequently, I am inclined to believe that the true explanation is much simpler, and that the change was due entirely to the fact that the patient had become thoroughly tired of the diet and régime to which she was being subjected and was suffering from anorexia. The weather, too, at this time had become very oppressive. Confirmation is lent to this belief in the fact that as soon as the patient left the hospital, and lived under home surroundings, her appetite returned and she again began to take her food with relish and increased rapidly in weight.

One very striking feature during the last week of this observation is the fact that in spite of the very low nitrogen intake, as well as the fact that she was losing in weight, she still had the capacity for storing nitrogen, though to a much less degree than during the three preceding weeks.

The second case in our series about corresponds, so far as the period of the pregnancy is concerned, to the case studied by Hoffström. Our patient went into labor, however, about a month before the expected date of confinement, so that observations were carried out only for the last 19 weeks of her pregnancy. That she was delivered about four weeks prematurely is, I think, evident when we consider her menstrual history, the time when the fœtal movements first became perceptible, as well as the fact that the child was somewhat under the average weight.

As is shown in the accompanying table (Table III), in which I have set down the daily average exchange, this patient was also found to be storing nitrogen from the time observations were begun. As in the preceding case, a chart of the actual daily nitrogen exchange was also kept, which shows that on occasional days, as in Case I, there was a slight negative nitrogen balance.

In studying these patients it was thought that possibly cyclical variations in the nitrogen exchange might be noted at periods of time corresponding to the time of the menstrual periods, had the patient not been pregnant, but such was not found to be the case.

Although this patient was at all times allowed sufficient food to satisfy her appetite, nevertheless, her daily intake throughout the entire period was strikingly low, at no time being greater than 12.5 gm. N. per day. Storage became particularly active from the nineteenth to the twenty-first weeks, at the time when fœtal movements were becoming particularly active.

The low nitrogen content of the feces is probably to be accounted for partly by the low nitrogen intake and partly by the easily digestible diet of the patient.

As in Hoffström's case, the most active storage took place during the last nine weeks of the pregnancy when the fœtal needs were at a maximum. The total nitrogen stored by this patient during the period of observation, amounted to 419.38 gm. N. It is interesting to try to determine what became of this nitrogenous material, although this, of course, can only be determined approximately.

The child weighed 2850 gm. Michel, in his analyses of human fœtuses, found the nitrogen content of a child weighing 3335 gm. to be 72.7 gm. N. Calculating on this basis, which in this case, however, can only be approximate, the nitrogen content of the child alone ought to be 62.1 gm.

The placenta was not analyzed. Its weight, without cord and membranes, was 500 gm. As shown by Koelker and Slemons, one-half of the fresh weight is made up of fœtal blood, whereas the weight of the dried, water-free material amounts to 7 per cent of the fresh weight of the organ, and the nitrogen content of this dried material to 14.9 per cent. Making use of these findings, we calculate that the nitrogen content of the placental tissue would be 5.21 gm. N., and upon adding to this the nitrogen content of the fœtal blood, which should amount to 9.45 gm., we estimate that the total nitrogen content of the organ is approximately 14.66 gm. We may allow 2 gm. (an extreme figure) as the nitrogen content of the cord and membranes, which weighed 40 gm.

Deducting the weight of the child, placenta and membranes, and blood lost at the time of delivery, from the total loss of weight of the patient at the time of labor, we find the amount of amniotic fluid to be approximately 540 gm. which, from the figures given by Hoffström, would contain 0.19 gm. N.

The nitrogen content of the ovum, then, may be tabulated as follows:

Child	62.10 gm. N.
Placenta	14.66 "
Cord and membranes	2.00 "
Amniotic fluid	0.19 gm.
Total nitrogen content of ovum	78.95 gm. N.

Hoffström estimates the nitrogen content of the entire ovum at the end of the seventeenth week of pregnancy to be 5.41 gm. Accepting this figure as being correct, we find then that, of the 419.38 gm. N. stored by this patient, 73.54 gm. have been diverted to the growth and development of the ovum. This leaves a balance of 345.84 gm. N. which have been added to the general maternal organism. From this amount, however, we ought to deduct the nitrogen content of the blood lost at the time of labor, and which amounted to 5.56 gm., leaving a balance of maternal storage of 340.28 gm.

A certain proportion of this has, of course, been utilized in the hypertrophy and development of the genital organs incident to the pregnancy, more particularly the uterus and breasts.

The uterus increases in size up to 800 or 1000 gm. Slemons found the nitrogen content of a uterus removed by supravaginal amputation following Cæsarean section, and weighing 850 gm. in the fresh state, to be 38.75 gm.

Assuming the hypertrophy of the breasts to amount to half a kilogram, this would account for approximately another 17 gm. N. We thus have approximately 55.75 gm. of the

maternal storage diverted to the development of the genital organs, but we still have left a balance of 284.53 gm. N. added to the maternal organism, which Hoffström describes as "Rest-material."

In the third patient, observations were begun at a rather later period, at approximately the twenty-fourth week of the pregnancy.

One very noticeable feature in this patient is the fact that her nitrogen intake was always greater than in the preceding case, at times almost double; and another very striking feature is the marked increase in the N. intake during the last five and a half weeks of the pregnancy. This was entirely voluntary on the part of the patient, and the diet was simply increased to the point of satisfying her appetite, no artificial element in the way of forced feeding being introduced. Her body-weight increased 16¾ pounds during the time of observation, as compared with 14½ pounds in Case II, during a somewhat longer period.

As in Case II, this patient was found to be storing nitrogen to a marked degree from the beginning of the observations (see Table IV), although she also showed an occasional slight negative balance in the actual daily exchange. The most active storage occurred during the last five and a half weeks of the pregnancy as compared with the last nine weeks in the preceding case, and this also corresponded to the time when the diet was at its maximum.

The total storage of nitrogen during the 14½ weeks the patient was under observation amounted to 336.21 gm.

Using the same basis for the calculations as in the preceding case, I have estimated below the amount of the stored nitrogen which has been diverted to the development of the ovum:

	Weight.	Nitrogen Content.
Child	2960 gm.	64.5 gm.
Placenta	420 "	11.73 "
Membranes and cord	60 "	2.0 "
Amniotic fluid	1845 "	0.68 "
Total		78.91 gm.

Hoffström estimates that the nitrogen content of the entire ovum at the end of the twenty-third week amounts to 14.26 gm. Of the 336.21 gm. of nitrogen stored, therefore, we then find that 64.65 gm. have been diverted to the growth and development of the ovum. In this patient, then, we have had 271.56 gm. N. added to the general maternal organism. Again deducting the nitrogen content of the blood lost at the time of delivery, and which amounted to 4.83 gm., we have a maternal balance of 266.73 gm. N.

If, as in the previous case, we allow 38.75 gm. N. for the development of the uterus, and 17 gm. N. for the breasts, we still have a maternal balance of 210.98 gm. N. as "Rest-material."

In these two cases, the amounts of nitrogen allowed for the development of the genitalia, and the estimated nitrogen content of the ovum are, of course, only approximate. However, I think they are sufficiently accurate to show us that, in normal human pregnancy, the storage of nitrogen by the maternal organism is far in excess of the actual needs of the developing ovum, and indeed may be several times the amount actually needed for its development.

As to the form in which the "Restmaterial" is stored, definite statements cannot be made as yet. A certain portion of it is doubtless made use of in the formation of new blood. As shown by Miller, Keith and Rowntree, the blood volume is very definitely increased at the end of pregnancy. Indeed, in Case III of this series the woman was one of the subjects of their observations, and at a time four weeks before her delivery the blood volume was estimated to be 5408 cc. This, however, would only account for a small portion of the "Restmaterial." A portion also is probably utilized in the hypertrophy of muscles and the various glandular structures affected by pregnancy. In regard to the remainder, Hoffström accepts the hypothesis that this is stored as unorganized protein, as a reserve material; and for the present, until definite proof in regard to its disposal can be adduced, this seems to offer a very plausible explanation.

This reserve is probably drawn upon extensively during the puerperium and period of lactation, during which the entire reserve supply is possibly exhausted.

Cases II and III of our series were both studied for periods of ten and seven days respectively after labor. Unfortunately the observations could not be carried on longer. The results obtained did not differ from those of Slemons and other observers. Both patients showed a negative nitrogen balance, decreased in weight, and both were losing nitrogen when the observations were brought to a close.

Ammonia and Amino-Acid Nitrogen.

In Case I, daily estimations of the ammonia nitrogen present in the urine were made by Folin's method, and its percentage was found to be practically normal; although on one occasion it made up 8.6 per cent of the total urinary nitrogen. The extremes were 2.8 per cent and 8.6 per cent, with an average for the time of observation of 4.8 per cent of the total nitrogen. The daily figures are shown in Table II (see also Chart I).

This is a somewhat lower average percentage of ammonia nitrogen than is generally present in the urine during late pregnancy, as Slemons and Murlin both found rather higher figures.

In this patient the free amino-nitrogen was also determined by the method of Van Slyke, on every daily total specimen of urine, except on five occasions. These daily percentages of amino-nitrogen are also shown in Table II, and are seen to be somewhat higher than those generally given for the non-pregnant individual (stated by Van Slyke to be about 1 to 1½ per cent of the total nitrogen). The extreme figures found were 2.0 per cent and 4.3 per cent of the total nitrogen, with an average of 2.97 per cent for the whole period of study. Landsberg, in his series of observations on ten pregnant women, found an average of 3.8 per cent of amino-nitrogen in the urine during the latter part of pregnancy, as compared with 2.8 per cent

in a series of non-pregnant individuals, his estimations being made by the formol-titration method. Falk and Hesky and Frey also found an apparent increase in the amino-nitrogen.

In Case II, daily estimations of the ammonia nitrogen were also made throughout the entire period during which the

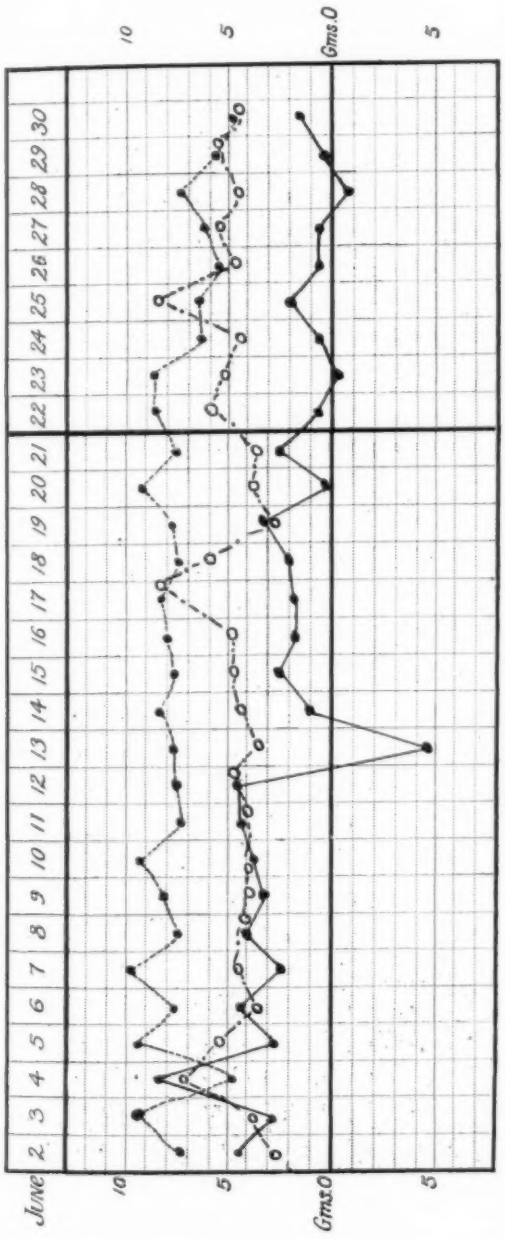
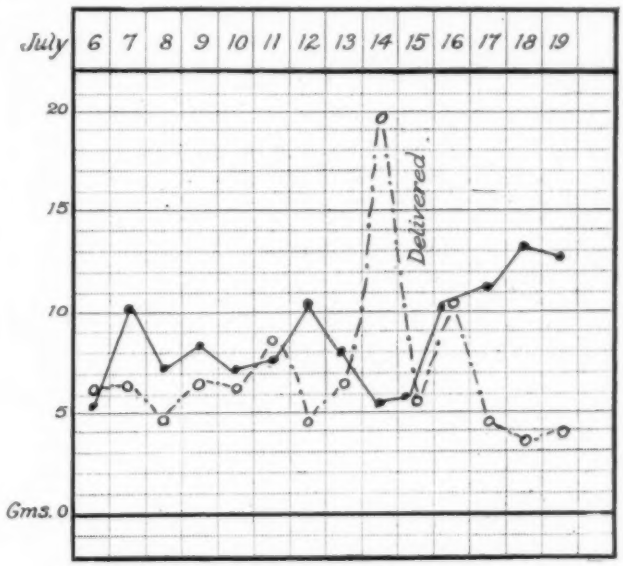


Chart I, Case I.

patient was under observation. In the earlier weeks, the results obtained about correspond to those in Case I and are well within normal limits. During the last six weeks of the pregnancy, however, there was a slight, but still a very definite, increase in the percentage of ammonia nitrogen, although this never reached what would be regarded as an abnormal figure. On the day on which labor began, July 14, there was a very pronounced increase in the percentage of ammonia nitrogen, which reached 19.8 per cent of the total urinary nitrogen.

The free amino-nitrogen of the urine was determined daily for a period of five weeks from the thirty-first to the thirty-fifth weeks inclusive. The highest figure obtained on any one day was 5 per cent and the lowest 1 per cent of the total urinary nitrogen, while the average daily percentage for the whole period was 2.56 per cent, which practically corresponds to the results obtained in Case I in the early weeks of pregnancy. The daily average ammonia nitrogen and amino-nitrogen percentages for each week are shown in Table V, and the daily percentage of ammonia nitrogen for the last 10 days of pregnancy and day of delivery are given in Chart II.

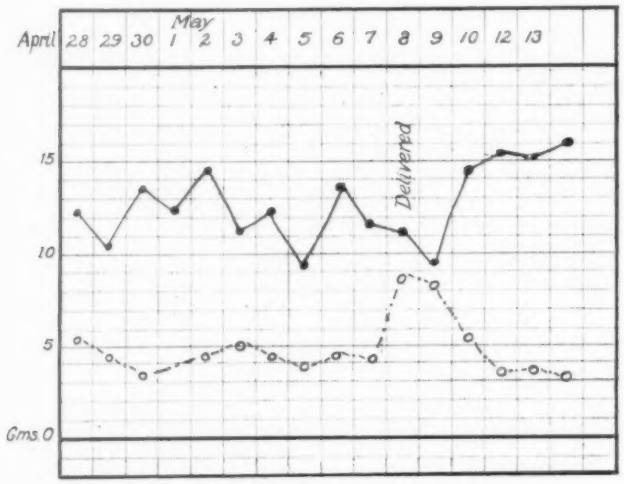


Total Urine N., in Gms. ●——●
% of Ammon. Nitrogen, o——.——o, showing rise before labor.

Chart II, Case II.

Daily estimations of the ammonia nitrogen in Case III also showed the percentage to be well within normal limits throughout the entire period. In this patient there was no decided increase during the last weeks of the pregnancy, as was noted in Case II, the ammonia percentage remaining remarkably constant throughout the entire period. The absence of such a rise in the ammonia percentage in this case is probably to be explained by certain differences in the diet of the two individuals, Case III ingesting and eliminating much larger amounts of nitrogen than did Case II; consequently, slight variations in the actual daily amount of ammonia eliminated would produce little or no change in the percentage of ammonia nitrogen. There was a decided rise, however, in the percentage of ammonia nitrogen on the day of delivery, reaching 8.6 per cent of the total nitrogen. The daily percentages of ammonia nitrogen for the last 10 days of pregnancy and

the day of delivery are shown in Chart III. The fact that this rise in percentage of ammonia nitrogen was found on the day of delivery in Case III, and on the day preceding delivery in Case II, is to be explained, I think, by the fact that in Case III



Total Urine N., in Gms. ●——●
% of Ammon. Nitrogen o——·——o, showing rise at labor.

CHART III, CASE III.

labor began shortly after the termination of a 24-hour period of observation, whereas in Case II labor had already been in progress for some hours before the 24-hour period had been completed, and in our studies it was not feasible to make analyses of the excreta at shorter intervals than 24 hours. In the cases

TABLE V, CASES II AND III.

DAILY AVERAGE PERCENTAGES OF AMMONIA NITROGEN AND AMINO-NITROGEN.

Case II.			Case III.		
Week.	Per cent of Ammonia N.	Per cent of Amino-N.	Week.	Per cent of Ammonia N.	Per cent of Amino-N.
18	5.66	....	....	....	....
19	4.80	....	....	....	....
20	4.70	....	....	....	....
21	4.64	....	....	....	....
22	4.64	....	....	....	....
23	3.70	....	....	....	....
24	3.98	....	24	5.50	1.82
25	5.22	....	25	4.67	1.75
26	5.02	....	26	4.45	2.24
27	4.70	....	27	4.35	....
28	5.32	....	28	3.94	....
29	4.76	....	29	3.82	....
30	5.80	....	30	3.87	....
31	6.45	3.14	31	3.90	....
32	5.57	2.48	32	3.60	....
33	6.31	1.98	33	3.60	....
34	6.85	2.07	34	4.00	....
35	6.20	3.13	35	4.24	....
36	8.76	....	36	4.50	....
37	....	....	37	4.50	....
38	....	....	38	4.10	....

studied by Slemons the highest percentages of ammonia nitrogen were found on the day of delivery, but in three of his cases there was also a very definite increase on the day preceding the onset of labor.

For the first three weeks this patient was under observation, daily estimations of the free amino-nitrogen were also made. Somewhat lower figures were obtained than in Cases I and II during the earlier and later weeks of pregnancy and a slighter degree of variation in the daily figures was noted. The extremes were 1.1 per cent and 3.2 per cent of the total urinary nitrogen, and the daily average for the three weeks was 1.9? per cent. The daily average percentages of ammonia and amino-nitrogen for the period during which observations were made are shown in Table V, together with the same figures for Case II.

From the observations made on the amino-nitrogen of the urine in our three patients at various periods of pregnancy, it would seem that there is a definite increase in the percentage of nitrogen eliminated in this form. This increase, however, is largely a relative one, the percentages being higher on account of the decrease in the total nitrogen of the urine.

CONCLUSIONS.

1. In the perfectly normal pregnant woman, storage of nitrogen begins at a much earlier period than has hitherto been supposed; possibly the organism may acquire the capacity for storing nitrogen from the very beginning of the pregnancy.

2. In the early months this storage is far in excess of the actual needs of the developing ovum, and the excess must be added to the general maternal organism.

3. Storage of nitrogen continues throughout the entire duration of pregnancy, being most marked during the last few weeks, when the fœtal needs are at a maximum.

4. The nitrogen stored is greatly in excess of the actual needs of the developing ovum, so that, apart from the amount needed for the hypertrophy and development of the genitalia and breasts, a large proportion of the nitrogen stored is added to the general maternal organism as "Restmaterial," though, concerning the form in which this reserve is stored, we are unable to make any positive statement. The nitrogen capital of the maternal organism is thus increased, though the reserve supply may possibly be entirely exhausted during the puerperium and period of lactation.

5. In the healthy woman, who goes through a normal pregnancy, the period of gestation does not necessarily represent a "sacrifice of the individual for the sake of the species," but may actually be a period of gain.

6. There is a relative increase in the percentage of urinary nitrogen excreted in the form of free amino-acids, though not necessarily an absolute increase in this form of nitrogen.

7. There is also a tendency for the percentage of ammonia nitrogen to become increased during the last weeks of pregnancy, although at other times during the pregnancy there is practically no variation from the percentages noted in non-pregnant individuals upon a similar diet.

In conclusion I wish to express my gratitude to Prof. J. Whitridge Williams for the privilege of carrying out this work; also to the various members of the resident obstetrical staff for much valuable assistance in supervising the régime under which these patients were kept.

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FUNCTIONAL SIGNIFICANCE OF MITOCHONDRIA IN TOXIC THYROID ADENOMATA.

PRELIMINARY REPORT.

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It has been customary in the past to group under the designation "thyroid adenomata" new growths of benign nature occurring in the thyroid gland in the form of rather well-defined nodules or even encapsulated tumors that are usually readily distinguishable from the adjoining normal thyroid parenchyma. These adenomata are further subdivided upon the basis of their histological structure into colloid, cystic and fœtal adenomata. Whether the latter are or are not suitable classifications I shall not discuss at the present time. The terms colloid and cystic are self-evident as applied to their structure, while in the case of those adenomata whose structure is exceedingly variable, and in which atrophic-looking, colloid parenchyma alternates with hyperplastic-looking parenchyma quite different from the ordinary thyroid structure, the term "fœtal adenoma" has been applied upon the assumption that these tumors had their origin in embryonic remnants.

The histological structure of these adenomata suggests in the majority of instances relative functional inactivity; that is, if the assumption of functional inactivity as compared with overactivity is based upon the histological criteria ordinarily applied to the study of the thyroid gland. The criteria of overactivity, namely, the increased height and size of the thyroid cells, the infolding and general hypertrophy and hyperplasia of the thyroid parenchyma and the diminished size of the acini containing little or no colloid, when applied to these adenomata, would lead one almost surely to the conclusion that in the absence of these criteria the tumor in question is an inactive one. Now it is just in these circumscribed tumors that one so frequently finds the parenchyma consisting in the main of low cuboidal or even flattened epithelium, with small, often pycnotic nuclei, a considerable, often very abundant amount of colloid, absence of infolding of the follicular epithelium and of evidence of hypertrophy and hyperplasia generally of the thyroid epithelium. In spite of these facts one frequently encounters clinical states of undoubted hyperthyroidism associated with the occurrence in the thyroid gland of such circumscribed nodules. The hyperthyroidism symptoms may be very mild and hardly perceptible, or in some instances they may be extreme. In certain cases, however, the thyroid lesion may be present without any discoverable symptoms pointing to a condition of hyperthyroidism. To explain these symptoms of thyroid overactivity many have assumed that as a result of the mechanical pressure exerted upon the adjoining normal thyroid gland, the secretion of the

latter has been squeezed in excessive amounts into the circulating fluids and has thus caused the symptoms of hyperthyroidism. Another explanation offered is that the mere presence of the tumor acts as a mechanical irritant to the gland, thus exciting the latter to overactivity. By others the symptoms of hyperthyroidism have not been explained at all, the statement simply being made that their origin must be looked for elsewhere than in disorders of the thyroid gland. And lastly, in some instances the adenoma was held responsible, despite the fact that no satisfactory histological evidence of its hyperactivity was apparent.

Patients with evidently inactive adenomata present themselves to the surgeon principally for the removal of the growth for cosmetic reasons or for the relief of mechanical pressure upon the trachea and œsophagus. It is a common experience in the other cases, those presenting symptoms of hyperthyroidism, that, after the surgical removal of the adenoma, such symptoms rapidly subside. This experience lends support to the assumption that the tumor itself is responsible for the symptoms of thyroid overactivity.

An example of this kind may be given, illustrative of conditions in other patients who have recently come for treatment to the surgical clinic of Professor Halsted. A thyroid tumor had existed for a number of years, at first unassociated with symptoms suggestive of hyperthyroidism, presenting, however, in the last year and a half definite symptoms of moderate thyroid intoxication. At operation upon the thyroid an encapsulated tumor was removed and upon histological examination was found to have the appearance of a simple inactive colloid adenoma (*cf.* photograph, Fig. 2). Furthermore, upon physical examination of the patient before operation, the thyroid gland itself did not present any findings suggestive of overactivity, such as increased vascularity; nor did the gland at operation suggest such a condition. Following the operation, however, there was a marked improvement in the patient's general condition. This fact goes to indicate that the adenoma must in large measure have been responsible for the production of the symptoms of hyperthyroidism.

The first patient illustrating these points, whom I had the privilege of observing, was one who came to the surgical clinic of the Peter Bent Brigham Hospital, Boston, Mass., March 11, 1914. It is for this reason and because of the fact that this case illustrates the findings in several recent cases admitted to the surgical clinic of The Johns Hopkins Hospital that I shall briefly review the history and examination.

The case was that of a married woman, aged 37 years, who complained of a *lump in her neck* (*cf.* Fig. 1), *recent difficulty in swallowing*, and *nervousness*. She was admitted to the surgical clinic of the Peter Bent Brigham Hospital, March 11, 1914.

The family history is unimportant. There has been no similar trouble in any of her ancestors.

Past History.—She had scarlet fever at the age of five years, but no other acute illness. She has occasionally suffered with headaches, sore throat and tonsillitis. She has had some dyspnœa. The digestion has always been good; the bowels have been constipated. The genito-urinary and menstrual histories are negative. She has had four children, living and well. Her husband was accidentally killed while at his work one and a half years before her admission to the hospital. She attributes the onset of her nervous symptoms to this cause. Her habits are good. *Weight*, March 18, 58.8 K. (129.3 pounds).

The *present illness* dates back five or six years, to a time just after the birth of her last child. She noticed that the neck was getting larger owing to the appearance of a lump in the lateral margin of the right thyroid lobe. The lump was very small at this time, perhaps the size of a marble. Two or three years ago there was a slight enlargement, and in the past four to five weeks the nodule has been growing more in the direction of the isthmus. The lump has never been painful and has never caused the patient any noticeable trouble until in the past four to five weeks, when there has been slight difficulty in swallowing. Slight hoarseness of the voice has also been noticed recently. *Slight palpitation* has been apparent for four or five years and has grown distinctly worse since the death of her husband a year and a half ago.

Symptoms of nervousness and worry have been present for the past two years, but have gotten distinctly worse following an attack of tonsillitis four weeks ago.

Increased perspiration, hot and cold flushes, salivation and *some loss of weight*, have also been noticed during the past four weeks. *Asthenia* and *loss of appetite* have been rather marked recently. *Constipation* has been troublesome for several years.

Physical Examination.—The positive findings, many of which point to a mild degree of hyperthyroidism, may be summarized as follows: The patient is a poorly nourished, restless, rather nervous, middle-aged woman.

There is increased perspiration of the palms of the hands, axillæ and soles of the feet.

Eyes.—The Möbius and Dalrymple signs are positive. There is a slight widening of the lid-slits, but no exophthalmos and no von Graefe's sign are apparent. The hair has tended to come out in increased amounts recently. There is some increased pigmentation of the skin.

Neck.—In the region of the right lobe and right half of the isthmus of the thyroid gland is an irregular prominent swelling, about the size of an egg. There is no enlargement of the left lobe. There is no venous distention of the superficial vessels to be noted and no apparent increase in the carotid pulsation or in the pulsation of the thyroid gland itself.

Measurements of the Neck.—

Circumference at level of thyroid cartilage	32 cm.
Circumference over middle of isthmus	35 cm.
Circumference at root of neck	36.5 cm.

Measurements of Nodule in Right Lobe and Isthmus.—

Transverse diameter	7.5 cm.
Vertical diameter	4.5 cm.

Palpation.—There are no thrills palpable over the poles of the thyroid gland or over the tumor itself. The tumor is circumscribed; it can be readily displaced upward into the neck and apparently arises from the right thyroid lobe. It is elastic to the feel, not fluctuant, and has the consistency of a colloid nodule. The left lobe of the thyroid gland is not distinctly palpable. The right lobe, aside from the nodule, is not distinctly palpable.

Auscultation.—No bruits are heard over the poles of the thyroid gland or over the tumor.

Teeth.—The few that remain are in bad condition. Most of the teeth have been extracted.

Chest.—No retrosternal dulness. Heart and lungs negative.

Mammary glands atrophic. Montgomery's glands hypertrophic.

Abdomen.—Edges of liver and spleen just felt. No epigastric pulsation. Adipose tissue lacking in the skin.

Extremities.—Perspiration of hands and feet noticeable. They are quite cold. No edema of legs.

Reflexes.—Superficial reflexes inactive. Deep reflexes active.

Tremor not characteristic. A slight unsteadiness in the hands is perceptible. The patient has been resting in bed for six weeks.

FIG. 1.—Photographs of the patient, showing the circumscribed tumor of the right lobe and isthmus of thyroid gland. Note the absence of exophthalmos.

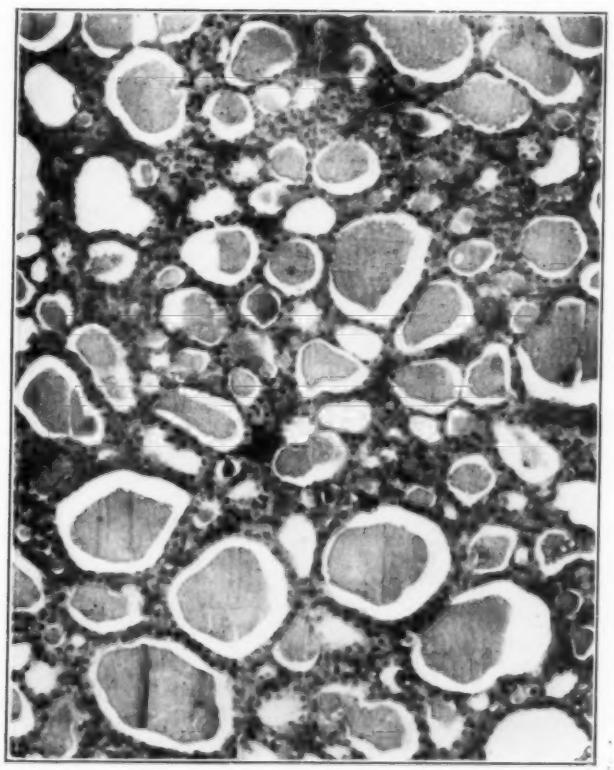

FIG. 2.—Photomicrograph (aqueous chrome-sublimate fixation, and hematoxylin-eosin stain; 4 mm. in thickness) of a section representative of the general appearance of the adenoma in the thyroid gland. Note the relatively large amounts of intrafollicular colloid and the absence of the common evidences of hypertrophy and hyperplasia of the thyroid epithelium. (× 100.)

Temperature varies between 97° and 98°.

Pulse averages about 70 per minute.

Urine negative. Output varies between 1300 and 1500 cc. in 24 hours.

Blood Examination.—W. B. C., 12,400; hæmoglobin, 78 per cent. The differential count shows no abnormal findings.

Blood Pressure.—Systolic, 120 mm. Hg.; diastolic, 74 mm. Hg.

Pharmaco-dynamic Tests.—The patient gives a practically negative response to the hypodermic injection of 0.00075 gm. of atropin. There was a marked response to the hypodermic injection of 0.0075 gm. of pilocarpine, especially evidenced by the profuse *perspiration*, *salivation* and *coldness* of the extremities produced. The pulse rate was somewhat diminished, but no change in the respirations or temperature was observed.

The tolerance to levulose by mouth is approximately 150 gms. Glucose 100 gms., when given by mouth and followed by the hypodermic administration of adrenalin 0.00075 gm., does not produce a glycosuria.

Operation.—March 21, 1914. *Excision of encapsulated fœtal adenoma in the right thyroid lobe and isthmus.*

The tumor was found to possess a definite capsule. It was inclosed within the normal-appearing right thyroid lobe, which was considerably thinned out over the tumor. The latter shelled out readily and was about the size of a small lemon. The left thyroid lobe was explored and gave all the appearances of being normal. There were no evidences of hypertrophy or hyperplasia of the thyroid gland, which also failed to show any evidence of increased vascularity.

Gross Pathological Examination.—The tumor is about the size of a small lemon. It possesses a distinct capsule and weighs 33 gms. Attached to it is a section of normal-appearing thyroid tissue. At the right border of the nodule is a separate distinct enlargement, the size of a cherry.

On cross-section the tumor is seen to be composed of a soft pulpy tissue, dark red in color; and interspersed in it are seen irregular islands of whitish, apparently hyperplastic tissue. In one area there is a small cyst, containing a thin straw-colored fluid and lined with a soft reddish granular tissue. In the wall of the cyst is a plaque of calcification. Other granules of calcification are seen scattered through the tumor. In certain areas the parenchyma contains a considerable amount of colloid. Nowhere is there apparent any normal-appearing thyroid gland. The smaller nodule on the right border of the tumor on cross-section is seen to consist of a pale yellowish parenchyma containing small whitish islands of tissue and a moderate amount of colloid.

Microscopic.—Fig. 2 (×100) represents a photomicrograph of an area typical of the greater portion, in fact, of almost the entire adenoma. In certain areas there are aggregations of small follicles, many of which lie free in a matrix of interacinar colloid. The latter does not seem to have resulted from traumatic rupture of intact follicles, for the follicles, in the areas in question, are not broken and there is no evidence of hemorrhage. The follicles vary in size, nowhere being extremely large. There are many small ones. Intrafollicular colloid is present in fairly abundant amount. The follicular epithelium is everywhere of the low-cuboidal and even in many cases of the flattened type, and nowhere is papillary infolding of the epithelium apparent. There are no signs of the characteristic hypertrophy and hyperplasia of the thyroid epithelium. Nowhere does one see tall, columnar epithelium. In certain areas between the larger follicles there are aggregations of smaller follicles, apparently newly formed. The cytoplasm of the cells on the whole is moderately abundant. It stains well with eosin, and in it, upon close observation, is seen a sprinkling of fine pink-staining granulations. (The latter upon subsequent study proved to be mitochondria.) The nuclei stain well in hæmatoxylin. They are vesicular, oval or flattened, and contain usually a well-marked centrosome and numerous dark-staining chromatin granules. The oval or flattened nuclei are most often pycnotic. There is no apparent increase in vascularity. Basing one's opinion upon these histological facts, one would conclude that the adenoma is functionally inactive.

Pathological Diagnosis.—"Fœtal adenoma" of the thyroid gland.

Upon examination 11 days after operation, except for some feeling of weakness and loss of appetite, the patient's general condition was considerably improved. There was definite improvement in her previous symptoms of *nervousness*, *palpitation*, *worry*, "*hot and cold flushes*," and increased *perspiration*. The pulse rate, which before operation was relatively slow, showed a slight fall, being occasionally as low as 65 per minute.

The temperature varied between 97.4° and 98.6°. The respirations were 20.

The skin was drier than before operation.

All the eye signs of exophthalmic goitre were negative, including the Möbius sign, which was positive before the operation. There was no unsteadiness of the eyeballs in the extreme lateral position.

There was no difficulty in swallowing.

The neck, except for the results of the extirpation of the gland, was as before operation.

Reflexes as before.

Tremor, none.

There had been a loss in weight of 1.3 K. (2.86 pounds) since the operation.

The responses to the hypodermic administration of atropin and pilocarpin in the same dosage as before operation were definitely less.

One year following operation patient reports that she weighs 142 pounds (a gain of 12.7 pounds), and that she has been definitely benefited by the operation. Her pulse rate is 62 per minute. There is no tremor. Slight nervousness and palpitation persist. She reports also that she is taking care of a large family, a fact to which she attributes several of the symptoms which still persist but to a milder degree than before.

To summarize, then, we have here an illustrative case of a woman of middle age who showed in the thyroid gland a circumscribed swelling which had been present for several years, apparently unassociated with any recognizable symptoms. In the last year and a half a number of symptoms of mild hyperthyroidism had supervened along with the history of more rapid enlargement of the nodule. Before and at operation the thyroid gland itself did not suggest the appearance of overactivity. After removal of the tumor, considerable benefit to the patient ensued not only from relief of mechanical pressure, but also in regard to the symptoms of hyperthyroidism. The gross and microscopic examinations of the customary kind did not reveal evidence of hyperactivity in the adenoma. In fact, the general appearance is represented in the low-power photograph (Fig. 2) of a hematoxylin and eosin section, which is quite characteristic of the whole adenoma.

In the absence of the common criteria of thyroid overactivity such as have been mentioned previously in this paper, there remained the possibility that, in spite of this absence, the activity of some or all of the cells of the adenoma might be in excess of the normal, thus producing an excessive amount of active thyroid principle. The latter could then be the cause of the symptoms of hyperthyroidism, and still, locally in the adenoma, there might be an absence of cellular hyperplasia and no diminution in the amount of stainable colloid in the follicles.

To determine this point it becomes necessary to demonstrate, if possible, by histological methods evidences of increased cellular activity. For this purpose a technique was employed which demonstrates clearly and fairly easily the presence, in the cell cytoplasm, of structures commonly known as mitochondria. The functional significance of the latter has been considered in a recent summary on this subject by E. V. Cowdry,[1] to which reference should be made for a complete account of these structures. I may say briefly that the mitochondria are structures occurring in the cytoplasm of all cells. They occur in the form of granules, rods or filaments. Observations made upon living cells in tissue cultures have furthermore shown that they may change their form. They were first observed by Altmann,[2] and more recently their functional significance has been more accurately studied. In their solubilities and staining reactions they resemble phospholipins and to a lesser extent albumins. They are undoubtedly closely related to the life process of the protoplasm of every living cell, and there is ample evidence that mitochondria play an active and fundamental rôle in cell activity.

A few facts that support this view may be mentioned. They are present in the cells not only of animals, but also of plants. They are more abundant in the active stages of the life of the cell and diminish progressively in number as the cells become senile. This is exemplified in the cells of the different layers of the skin. In the deeper layer where cell division and growth are more rapid, the mitochondria are not numerous, while in the more superficial cells, those either dead or dying, the mitochondria are either very few in number or entirely absent. Moreover, the mitochondria decrease in number as one passes from nucleated to non-nucleated red blood cells. It is well known also that mitochondria are particularly abundant in immature embryonic cells, in which metabolic processes are very active. Romeis[3] has found that mitochondria are very numerous in actively regenerating tissues. He used the term plasmosomes, a synonym for mitochondria. They have been observed, furthermore, to be increased in number in kidney cells after the administration of phloridzin. Other facts could be cited, which have been advanced by investigators to support the view that mitochondria participate in the processes involved in cell activity and metabolism. By some the mitochondria are said to be transformed into zymogen granules as in the pancreas, and thus to be the antecedents of the specific secretion of glandular cells.

In accordance with these facts it would seem probable that in glandular cells that are the site of increased secretory activity we should find in the cytoplasm an increased number of mitochondria over the normal. To determine this point a technique which has been devised by Bensley[4] was applied to the adenoma and to the adjoining normal thyroid tissue with the results to be described. Before discussing the latter I should like to mention a word in regard to this method. The tissue to be examined should be absolutely fresh, and placed in the fixation fluid in small pieces immediately after removal from the body. If this precaution is observed and the technical steps recommended by Bensley are carefully followed, no difficulty should be experienced in obtaining satisfactory results. The fixation fluid is an osmic-acid, bichromate of potash and acetic acid mixture, and the subsequent staining consists in the application, after mordanting with potassium permanganate, of acid fuchsin with a counter-stain of methyl-green. The sections should be less than 5 micra thick. The mitochondria are stained a brilliant red and are readily recognized, particularly with a sharp counter-stain such as methyl-green.

Now when the normal thyroid tissue adjoining the adenoma is studied after this technique has been applied, a picture resembling that illustrated in Fig. 3, as drawn by Miss E. Norris, is obtained. The mitochondria, staining a brilliant red in acid-fuchsin, appear in lower power magnification as small granules, but under the higher power oil-immersion lens they appear as short thick filaments or rods. They are scattered fairly uniformly throughout the cell cytoplasm which is rather scant in amount. In the more flattened cells the mitochondria are more abundant at either side of the nucleus, but in the cells provided with a greater amount of cytoplasm they occur also along the lumen border of the cell. Relatively rarely one sees cells in which the mitochondrial content is more abundant. In the space between the follicles, small aggregations of thyroid cells, without formation of acini but with the average number of mitochondria, are seen. The cytoplasm, scanty in amount, stains a faint green. The nuclei are vesicular in shape, stain faintly green, and often show the presence of nucleoli, which take on a darker green color.

The intrafollicular colloid stains homogeneously and appears light green which is often tinted a pink color, due to the amount of differentiation of the section in methyl-green or probably also to the age of the colloid. The latter, whenever present in the smaller, apparently younger follicles, is always greenish in color. No extrafollicular colloid was seen in the normal thyroid tissue.

If now we compare this picture with that obtained after applying precisely the same technique to the adenoma, results are obtained which are illustrated in Fig. 4. These appearances are quite characteristic of sections made from small blocks of tissue taken from numerous different areas in the adenoma. The mitochondria present essentially the same morphological features as in the normal gland. The strikingly greater abundance of the mitochondria everywhere in the sections of the adenoma, as compared with the normal gland, is at once apparent. This is true of practically all of the parenchymal cells regardless of whether these cells are tall columnar and contain a relatively abundant cytoplasm or whether they are flattened and poor in protoplasm. The cells themselves vary markedly in shape and size. Some are large

[1] Cowdry, E. V.: The General Functional Significance of Mitochondria. Am. Jour. Anat., May, 1916, XIX.

[2] Altmann, R.: Die Elementarorganismen, 1890. Leipzig, Veit & Comp., p. 145.

[3] Romeis, B.: Das Verhalten der Plasmosomen bei der Regeneration. Anat. Anz., 1913, XLV, 1-19.

[4] Bensley, R. R.: Studies on the Pancreas of the Guinea-pig. Am. Jour. Anat., 1911, XII, 308.

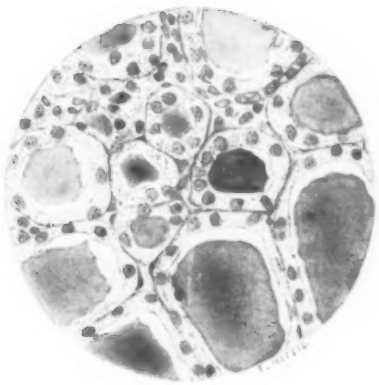

FIG. 3.—Drawing of section (4 mm. thickness) representative of the appearance of the normal right thyroid lobe adjacent to the fœtal adenoma. Note the relatively small number of mitochondria in the thyroid cells. (Acetic-osmic-bichromate fixation. Acid-fuchsin-methyl green. × 390. Oil immersion.)

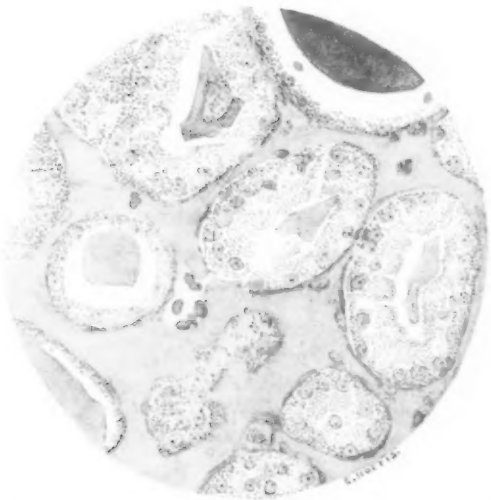

FIG. 4.—Drawing of section (4 mm. thickness) of "fœtal adenoma" in right thyroid lobe and isthmus, to show the relatively large numbers of mitochondria in the parenchymal cells as compared with the adjoining normal thyroid cells (cf. Fig. 3). Note also the large amount of extra-follicular colloid. × 390. (Technique same as in Fig. 3.)

and columnar; the greater number are low and cuboidal; and others are very much thinned out by pressure of the colloid contained within the follicles. Even the cells of the last type, presenting much the same appearance as the atrophic cells of an inactive colloid goitre, are rich in mitochondria.

The nuclei are on the whole slightly larger and somewhat richer in chromatin. The staining characters of nuclei and cytoplasm are in general the same in each instance. The intra- and extra-follicular colloid stains a homogeneous light green color. In several of the latter, desquamated parenchymal cells are seen containing great numbers of mitochondria. In some areas outside of the follicles colloid is seen in rather large amounts. Here and there solid groups of thyroid cells are seen, with no indication of follicle formation and containing great numbers of mitochondria.

That analogous conditions are probably present in animal pathology was indicated to me recently in the study of a tumor of a dog's thyroid brought to me by G. B. Wislocki. A circumscribed encapsulated tumor, the size of a cherry, was found enclosed in the center of an otherwise normal-looking thyroid lobe. The findings in the gross and in the general microscopic examinations of the gland were much the same as those occurring in a somewhat similar case described and illustrated by Goodpasture and Wislocki,[5] in their study of the relationship in dogs of old age to cell-overgrowth and cancer. In the present instance, however, there was no degeneration to be observed in the center of the adenoma. The latter was in all likelihood a hyperactive adenoma, for, as compared with the surrounding normal thyroid tissue, it contained in its parenchymal cells mitochondria in far greater number. Furthermore, there was in this case a moderate hyperplasia of the usual type. It would seem from this that there is reason for believing that hyperthyroidism symptoms might readily occur, in the dog as in man, in cases of similar pathological involvement of the thyroid gland.

In contradistinction to the case reported here, I have observed several instances of encapsulated thyroid adenomata, unassociated with symptoms of hyperthyroidism, and with no increase, in fact rather a decrease, in the number of mitochondria present in the follicular cells. In three recent cases of thyroid adenomata associated with marked symptoms of hyperthyroidism, but without exophthalmos, the parenchymal cells have shown a great increase in the number of mitochondria in their cytoplasm. Another evidence, empirical perhaps, that the adenomata of this latter class are hyperactive, is shown by the subsidence of the symptoms of hyperthyroidism almost immediately after the surgical removal of this tissue so excessively rich in mitochondria.

It is evident then that a method or technique is needed that will give us the means for determining whether the individual thyroid cells are functionally hyperactive or not, for without it and with reliance placed solely upon the older criteria of hyperactivity as pointed out above, many clinical cases of hyperthyroidism cannot be correlated with the histological appearance or changes occurring in the thyroid gland. It is the purpose of this preliminary report to call attention to the value of, and the need for, finer cytological studies in determining glandular function, especially in a gland presenting so many variations in its pathological anatomy as the thyroid gland. It is further felt that in the study of the pathological anatomy of the thyroid gland, the mitochondria will prove to be a better index of thyroid activity than the histological criteria heretofore applied. Since the mitochondria occur normally in the thyroid cell, and since they are present in greatly increased numbers in the adenomata associated with symptoms of hyperthyroidism, it would seem probable that they are correlated with an overproduction of an otherwise normal secretion produced by the thyroid cell. It is interesting to speculate why exophthalmos is so rarely if ever associated with thyroid adenomata. It may be that there is a very different form of intoxication in the true Basedow's disease. In the latter the thyroid gland, just as in the case of the toxic adenomata, shows a marked increase in mitochondria over the normal. There are, however, several differences in these two conditions in the number, morphology, size and distribution of the mitochondria, a description of which will be given in a later report. Interesting results will undoubtedly be obtained when studies are made on the occurrence of mitochondria in hyperplasias and pathologic new-growths occurring elsewhere than in the thyroid gland.

[5] Goodpasture, E. W., and Wislocki, G. B.: Old Age in Relation to Cell-overgrowth and Cancer. Jour. Med. Research, XXXIII, No. 3, p. 473.

RENAL DIABETES.[1]

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AND
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From time to time there have appeared in medical literature reports of "renal diabetes." Under this term is understood a glycosuria which is the result of an abnormal permeability of the kidney to sugar. The kidney in this pathological state allows a small amount of sugar to escape constantly in the urine, while the blood sugar maintains a normal level of between 0.07 and 0.11 per cent. The body has lost none of its power to utilize carbohydrate and hyperglycæmia is not found as it is in true diabetes mellitus. Consequently, an increase or decrease of the carbohydrate constituents of the diet has little effect on the percentage of sugar in the blood or the quantity excreted in the urine. These cases have none of the clinical

[1] From the Medical Clinic of The Johns Hopkins Hospital.

manifestations of diabetes mellitus, due either to a diminished ability of the body to utilize glucose or to the presence of a hyperglycæmia; there is no polydipsia, polyphagia or polyuria, no loss of weight or weakness, no pruritus or furunculosis, nor any other symptom of the disease. According to the present conception of this condition, it remains stationary, the glycosuria showing no tendency to increase, nor does diabetes mellitus develop from it; the subject continues in good health and without any abnormal symptoms or signs except a constant low-grade glycosuria. The data necessary for the diagnosis of renal diabetes are very few in number but sharply defined:

1. A glycosuria, maintained at a fairly constant level and not markedly affected by changes in the carbohydrate content of the food.

2. A normal percentage of blood sugar while the urine contains glucose.

From this description, it is evident that the term "renal diabetes" is a misnomer and that "renal glycosuria" would be more appropriate.

Thus far, very few cases of this interesting anomaly have been reported. Von Noorden,[2] in his monograph on diabetes mellitus, does not consider the symptom-complex of renal diabetes to be firmly established. His skepticism is no doubt due to the small number of cases on record. Allen,[3] in his recent thorough summary, "Glycosuria and Diabetes," admits two cases, those of Bonniger[4] and Tachau,[5] as indisputable examples of this condition. Since that time, several other instances of apparent abnormal permeability of the kidney to glucose have been published. Bonniger[6] observed a man, aged 37, who on life insurance examination two years previously had shown a glycosuria. After 10 days of irregular sugar excretion, probably influenced by severe alcoholic poisoning, the urine on 33 subsequent days was remarkably constant in its glucose content, which varied within the narrow limits of 0.1 to 0.5 per cent. These percentages were maintained on a carbohydrate-free diet as well as when the food contained an ample amount of the usual starches or included 100 gm. of dextrose or cane sugar. The urine collected in four or five specimens during the 24 hours for a period of eight days showed the same quantity of sugar (0.1 to 0.6 per cent) in each sample. The blood sugar was 0.08 per cent; some time later it was 0.06 per cent, and the urine which was voided before and after the latter determination contained 0.5 per cent of glucose. Bonniger[7] subsequently reports that this case has been observed for six years (eight years since glycosuria was demonstrated by life insurance examination), that he still excretes small amounts of sugar, and is in perfect health. The son of the patient is also afflicted with renal diabetes.

This case furnishes a convincing illustration of the existence of renal diabetes, provided that the sugar excreted was glucose. The blood sugar is normal, the glycosuria is constant and does not vary in direct proportion to the ingestion of carbohydrates, the disease is not progressive, and, finally, its hereditary character, upon which some authors have laid stress, is noted. The instances of this condition subsequently reported have shown that the intensity of the glycosuria is to a great extent, but not absolutely, independent of the carbohydrate intake. This is seen in our patient and is very evident in the following case, which was published by Tachau:[5]

E., aged 21, merchant, suffering with transient acute nephritis and gastro-enteritis following an excessive indulgence in fruit.

Days observed.	Diet.	Urinary glucose, gm. in 24 hours.
4	Carbohydrate free	0
6	Mixed (158 to 250 gm. carbohydrate)	0
15	Mixed (124 to 412 gm. carbohydrate)	1.1 to 6.0
3	Mixed plus 100 gm. dextrose.....	0.6 to 4.2

The days are grouped according to diet and the presence or absence of glycosuria and are not placed in chronological order.

Blood sugar determinations in per cent:

Fasting .....0.085 and 0.086
After breakfast 0.061
1 hour after 100 gm. dextrose..0.076, 0.109 and 0.082

The absence of glycosuria on some of these days can probably be explained by the fact that the level of the blood sugar varied at times and was on occasion depressed below the kidney threshold for this substance. It is known from the publications of Jacobson,[9] Strouse[10] and others, that there is a distinct rise of the blood sugar after meals. Since there is a universal tendency to hyperglycæmia after meals, slight fluctuations in glycosuria are to be expected in typical instances of renal diabetes. The criterion of an absolutely constant quantity of urinary dextrose cannot, therefore, be insisted on.

Other cases, which are considered to be true examples of renal diabetes have been brought forward by Graham[11] and de Langen.[12] The reports of Frank,[13] Rogue and Chalier[14] and Solomon[15] either lack sufficient data to establish the diagnosis of renal diabetes, or, as in some of Solomon's patients, appear to belong to cases of mild diabetes mellitus. Frank's exposition of increased renal permeability during pregnancy and after poisoning with mercury, uranium, chromium and cantharidin confirms the work of many investigators and furnishes suggestive evidence of the existence of a permanent renal glycosuria.

The question presents itself, why the renal barrier to sugar should be only slightly depressed, causing a renal glycosuria of such mild degree, and why the kidney threshold should not be more markedly lowered in some individuals, and conditions re-

[2] Von Noorden: Die Zuckerkrankheit, Berlin, 1912, S. 37.
[3] Allen: Glycosuria and Diabetes, Boston, 1913, p. 544.
[4] Bonniger: Deutsche Med. Wchnschr., 1908, XXXIV, 780.
[5] Tachau: Deutsch. Arch. f. klin. Med., 1911, CIV, 448.
[6] Bonniger: *L. c.*
[7] Bonniger: Verhandl. d. Cong. f. inn. Med., 1913, XXX, 178.
[9] Jacobson: Biochem. Ztschr., 1913, LVI, 471.
[10] Strouse, Stein and Wiseley: Bull. Johns Hopkins Hosp., 1915, XXVI, 211.
[11] Graham: Jour. Physiol., 1915, XLIX, p. XLVI (Proceedings).
[12] de Langen: Berl. klin. Wchnschr., 1914, LI, 1792.
[13] Frank: Arch. f. exper. Path. u. Pharmakol., 1913, LXXII, 387.
[14] Rogue and Chalier: Arch. d. mal de l'apparat digest., 1912, VI, 661.
[15] Solomon: Deutsche Med. Wchnschr., 1914, XL, 217.

sembling phlorizin glycosuria be found? It is very likely that such instances do occur, but have hitherto usually been confounded with true diabetes. One example of such a case, however, is on record. Galambos[16] cites the following data of a patient, a man 50 years old, who has suffered with polyuria and polydipsia ever since he can remember. Observation was carried on over a period of 21 days during which time the glycosuria varied between 66 and 198 gm., and the concentration of urinary dextrose between 2.6 and 7.4 per cent. The carbohydrate content of the diet was between 50 and 354 gm. Frequent collections of urine in this case showed a marked constancy in the hourly excretion of glucose; the administration of 150 gm. of dextrose did not result in any marked deviation from this regularity; on a day during which the 24-hour specimen was collected in five separate portions, it was found, on making the proper calculations, that 6.4, 4.4, 6.6, 4.8 and 6.6 gm. of glucose were excreted per hour in the various periods. These quantities are very much larger than in any of the cases hitherto reported. The blood sugar values, in per cent, were: During fasting, 0.09 and 0.05; 1½ hours after oatmeal feeding, 0.07; and 1½ hours after taking 100 gm. of dextrose, 0.17. The last figure is slightly above that which would be expected in most normal individuals,[17] but is not sufficiently high to invalidate the conclusion that this case is one of renal diabetes. There was a considerable degree of acidosis. This is only to be expected with the enormous losses of glucose in the urine; the carbohydrate balance between intake and output was often negative. This case, therefore, illustrates the possibility of a renal diabetes of severe type, a type which approaches in its characteristics the phenomena observed in phlorizin poisoning. Whether this patient presents an extremely rare anomaly or a condition of more frequent occurrence than has hitherto been suspected can be determined only through further study.

The number of published cases of renal glycosuria or diabetes which stand the test of closer investigation have been relatively few. The following record may, therefore, be of interest:

W. P. W., Medical History No. 34774, male, white, age 29, born in the United States, a station agent, descended from Anglo-Saxon ancestry.

Family History.—Father (aged 60), mother (aged 50), 1 brother and 4 sisters are all alive and in good health; one sister died of erysipelas. With the exception of marked obesity in one grandmother and several of her sisters, there is no history of hereditary disease; diabetes mellitus, heart trouble, kidney disease, apoplexy, gout, exophthalmic goitre and tuberculosis have never been found in the patient's family.

Habits.—Smokes 5 to 6 pipes a day; does not use alcohol; eats a considerable amount of bread but no excess of sweets.

Past History.—Measles and whooping cough in childhood, malaria 18 years ago, pneumonia 17 years ago, varicella, complicated by otitis media on the right side, 15 years ago. Venereal infection is denied.

Present History.—Three years ago passed a life insurance examination. This is the only urinary test remembered, until six weeks ago, when the patient applied to his physician for relief from backache. At that time, a glycosuria was demonstrated. The backache cleared up shortly; the glycosuria persisted in spite of a restriction of the carbohydrates in the food. There never have been any other symptoms pointing to diabetes mellitus with the exception of transient paresthesia of the fingers (no loss of weight or strength, no polyuria, polydipsia or polyphagia, no skin involvement—pruritus, furunculosis or other condition—no muscular cramps, no pains in the extremities); there have been no evidences of pancreatic disease (no pain in the epigastrium, no fatty diarrhea); all indications of exophthalmic goitre have been completely lacking at all times (no exophthalmos, no thyroid enlargement, no vomiting, nervousness, cardiac palpitation or diarrhea); there have been no signs of acromegaly or gigantism pointing to hypophyseal involvement; there has been no history of a renal lesion (no headache, visual disturbance, dyspnea, vertigo, edema or albuminuria); there has never been any skin pigmentation to suggest a cirrhosis of the pancreas and liver, that is, a hemachromatosis.

For the last two or three years there has been a tendency to increased frequency of urination during the day but not at night. The quantities voided have apparently not exceeded normal. This is evidently a pollakiuria rather than a polyuria, which is borne out by the ward observations which will be detailed further on.

There has been a slight chronic cough associated with a moderate nasal catarrh and mouth breathing. There have been no night sweats, hemoptysis or "pleuritic pain."

Present Complaint.—The patient feels perfectly well and would not believe himself sick were it not for the persistent, "sugar in the urine."

Physicial Examination.—Height 5 feet 9¾ inches, weight 152 pounds; appears to be in the best of health and spirits; the skin and mucous membranes are not pigmented, their color is normal, they are as moist as those of a normal individual. The pupils are equal and react to light and accommodation; von Graefe's sign is absent. The pharynx is injected and there is a moderate degree of nasal obstruction, as indicated by persistent mouth breathing. The tonsils are not enlarged or inflamed. There is no pyorrhea alveolaris. The thyroid is barely palpable. The pulse rate averages 75; the pulse is regular in force and frequency and of normal volume. The radial artery can be rolled under the palpating finger, but is soft and elastic. The temperature is normal. The respiratory rate ranges from 16 to 24. The systolic blood pressure is 140, the diastolic 80. The heart's apex beat cannot be seen, it is barely palpable in the fifth interspace, 10 cm. to the left of the median line; the character of the apex impulse is a normal one; there are no thrills over the precordium; the area of relative cardiac dullness extends 3.5 cm. to the right of the mid-line in the fourth space, and 10.5 cm. to the left in the fifth; the heart sounds reveal no murmurs, the second sound over the aortic area is somewhat intensified and is louder than the pulmonic second sound. The lungs are normal except for slight dullness and somewhat prolonged expiration in the right supraspinous fossa, and at times a few dry râles, after coughing, over the same area. The liver and spleen are not palpable and there are no areas of tenderness or increased resistance over the abdomen. The patellar reflexes are very active. There is no edema of the face, back or extremities. On the left thigh there is a small eczematous patch furrowed by scratch marks. The superficial lymph nodes are not enlarged. The hemoglobin is 100 per cent (Sahli), the red blood cells are 4,600,000 and the white blood cells are 8450 per cu. mm. The Wassermann test is negative. The urine on admission is clear, of reddish yellow color, specific gravity 1035, acid in reaction, negative for albumin, gives a distinct reaction for sugar, and on microscopic examination yields no casts or red blood cells; the qualitative tests for acetone and diacetic acid are negative; the phthalein test shows an excretion of 42 per cent in two hours; Ambard's constant determined at various times is 0.07, 0.11, 0.08, 0.10.

[16] Galambos: Deutsche Med. Wchnschr., 1914, XL, 1301.

[17] Jacobson: *L. c.*

Impression.—The presence of glycosuria was well established. The urine gave a positive reaction with both the quantitative and qualitative Fehling-Benedict reagent, yielded gas on fermentation with yeast, and the unfermented urine rotated the polariscope to the right. The nature of the glycosuria will be subsequently discussed. There may have been a healed tubercular lesion at the right apex; impaired resonance, slightly prolonged expiration and inconstant râles in this region are not pathognomonic of a tuberculous focus; it is certain that in the absence of fever, sputum, night sweats, chills and loss of weight an active process is not probable and therefore of no significance in explaining the glycosuria. Of equally little importance is the nasal obstruction and pharyngitis. The kidneys are anatomically intact as far as the physical and urinary signs are concerned; the functional tests of these organs, however, reveal some impairment as shown by a slightly diminished phthalein excretion and an Ambard's constant barely within what has been in our experience the upper normal figure. The connection between such a diminished kidney function and a possible renal diabetes are of extreme interest. The small eczematous patch in this case could not be regarded as a complication of diabetes mellitus, since the hyperglycæmia, which is the direct etiological factor of such a condition, was lacking.

The urinary nitrogen was determined by the Kjeldahl process, the ammonia according to Folin,[18] the glucose by Benedict's modification of Fehling's method,[19] the acid bodies by Shaffer's procedure.[20] The method of Lewis and Benedict [21] was used in estimating the blood sugar.

In this case the blood sugar levels were normal, though the urine voided at the same time that the blood specimens were taken invariably contained glucose. The first three determinations showed a slight tendency towards a hyperglycæmia, 0.11 to 0.13 per cent; these figures are probably too high, since, as noted in the foot-note to Table 1, the standard used to obtain them was at fault. This supposition is confirmed by the fact that the 18 subsequent results, unless they were carried out at times when abnormal amounts of sugar had been added to the diet, were strictly within normal limits, being either 0.09 per cent or less. It is known that the level of blood sugar in diabetes mellitus after the ingestion of glucose assumes a course different from that in normal individuals and presumably in those afflicted with a renal diabetes. In the present instance (Table 2) after the ingestion of 100 gm. of glucose, a hyperglycæmia of 0.15 per cent was evident within 35 minutes; two hours and five minutes after the experiment was begun, the blood sugar level returned to normal and subsequently became depressed below this figure. This is almost an exact duplicate of the curve which Jacobson [22] produced in normal persons under similar circumstances—a hyperglycæmia of an average duration of two hours, a rise of the blood sugar, which reaches its maximum in about 30 minutes, and in many cases a hypoglycæmia following the hyperglycæmia. The maximum blood sugar values obtained by this author after this test varied from 0.12 to 0.23 per cent. In diabetes Jacobson found somewhat the same results after the ingestion of 50 gm. of bread and it is only fair to assume that the figures would have been very much exaggerated had 100 gm. of glucose been taken instead. Table 3 demonstrates very clearly how the urine in the present case invariably contains sugar, rising as high as 2.2 per cent while the blood sugar maintains a normal level.

The urinary sugar is considerably reduced by restricting the carbohydrates of the diet, but is completely absent only after six days of starvation (Table 1) and reappears with a minimum amount of food. In diabetic patients exhibiting 11 to 13 gm. of glucose in the urine on a mixed diet, a sugar-free state has regularly been obtained after one or two days of starvation. That the amount of dextrose excreted is somewhat dependent on the diet, but to a very much less degree than in true diabetes, is seen in this instance as well as in some of the cases previously reported. Furthermore, it may be noted from Tables 1 and 3 that glycosuria was below 12 gm. on all the days when the diet was restricted, but reached 30 gm. when the carbohydrate intake was raised. The two-hourly specimens (Table 3) showed a marked constancy in the amount of sugar eliminated during each day. Here again the amounts varied to some extent in direct proportion with the starchy content of the food. This is accentuated in the urinary collections of October 20-21 and October 21-22, in which 0.5 gm. of glucose was excreted per hour at night, as compared with 0.8 to 2.7 gm. during the day. The direct effect of raising the blood sugar by carbohydrates is thus shown, since the kidney which is permeable to glucose at a subnormal level acts as an indicator of a normal blood sugar increase after meals.

The intensity of the acidosis during starvation, as shown by the quantitative and qualitative tests for the acid substances and the ammonia nitrogen ratio, is moderate in extent. It is difficult to interpret such a finding as indicative either of a true diabetes mellitus or of its absence. That acidosis occurs in normal individuals on carbohydrate as well as on total starvation, is a well-known fact. The observations made on fasting diabetics have shown that in some individuals the acidosis disappears rather promptly, while in others, especially the obese cases, it does not.[23] This has also been our experience. The interpretation of acidosis in fasting diabetics is especially obscure, not only because different patients show varying results due to their own constitutional peculiarities, but also because the procedure of fasting in diabetes, as practiced up to the present, has demanded the administration of broth, alcohol and bicarbonate of soda, all of which may either increase or diminish the excretion of acid substances. The studies in this instance would, therefore, make it possible to place this patient either in the category of those suffering with diabetes mellitus or those presenting a normal carbohydrate metabolism.

An attempt was made in our case to check the renal glycosuria by means of calcium chloride. Injections of this drug diminish the permeability of the kidney to glucose.[24] Fifteen

[18] Folin: Ztschr. f. physiol. Chem., 1902, XXXVII, 161.
[19] Benedict: Jour. Biol. Chem., 1911, IX, 57.
[20] Shaffer: Jour. Biol. Chem., 1908, V, 211.
[21] Lewis and Benedict: Jour. Biol. Chem., 1915, XX, 61.
[22] Jacobson: *L. c.*
[23] Joslin: Am. Jour. Med. Sc., 1915, CL, 485.
Allen: New York State Jour. Med., 1915, XV, 330.
[24] Underhill and Closson: Am. Jour. Physiol., XV, 321.

TABLE 1. URINE ANALYSES, BLOOD SUGAR DETERMINATIONS AND DIET.

Date.	Urine—24 hours. Volume in cc.	Total N., gm.	Ammonia, gm.	Ammonia N. as per cent of total N.	† Acetone.	† Diacetic acid.	Total acid substances as β. oxybutyric acid, gm.	Glucose. Per cent.	Glucose. gm.	Blood sugar, per cent.	Diet. ‡ Protein, gm.	Fat, gm.	Carbohydrate, gm.	Calories.	Weight, lbs.	Remarks.
Sept. 29–30	630	6.43	0.56	7.2	0	0	....	2.07	13.1	....	+	+	+	+	152	"Ward Light" diet.
30– 1	830	6.76	0.50	6.0	0	0	....	1.34	11.1	*0.13	+	+	+	+	....	" " "
Oct. 1– 2	750	8.34	0.58	5.8	0	0	....	1.58	11.9	....	0	0	0	0	....	Starvation.
2– 3	455	9.93	0.52	4.4	++	+	2.33	1.10	6.1	....	0	0	0	0	....	"
3– 4	550	12.12	0.76	5.2	+++	++	2.87	0.90	5.0	....	0	0	0	0	144	"
4– 5	485	10.13	0.97	7.9	++++	+++	2.54	0.56	2.7	*0.11	0	0	0	0	....	"
5– 6	700	13.37	1.64	10.2	+++	++	5.54	0.10	0.7	....	0	0	0	0	....	"
6– 7	590	10.77	1.56	12.0	+++	++	4.28	0.36	2.1	*0.11	0	0	0	0	138	"
7– 8	455	8.11	1.13	11.6	++++	+++	3.80	0.0	0.0	....	12	0	3	62	138	
8– 9	580	9.68	1.39	11.9	+++	++	2.49	Trace.	Trace.	....	21	14	7	245	136	
9–10	645	10.30	1.31	10.5	++	+	1.82	0.66	4.3	....	23	16	14	301	137	
10–11	550	7.70	0.99	10.5	++	+	1.59	0.63	3.5	....	23	19	14	328	137½	
11–12	785	9.64	1.36	11.6	+++	++	3.52	0.66	5.2	....	25	16	14	309	138½	
12–13	1495	5.17	1.01	16.2	+++	++	1.06	0.80	11.9	0.09	25	16	14	309	138½	
13–14	2378	....	....	....	++	+	0.93	0.27	6.5	....	78	44	15	791	137½	
14–15	1635	10.43	1.98	15.7	+	+	....	+	+	....	101	151	15	1880	137½	
15–16	1496	15.13	....	....	+	0	....	0.98	14.7	0.09	127	133	28	1846	....	
16–17	1373	12.91	....	....	+	0	....	1.21	16.6	0.09	144	145	94	2314	138½	
17–18	1440	13.70	1.14	6.9	+	0	....	1.60	23.0	0.09	139	216	126	3095	138½	
18–19	1230	11.79	1.23	8.7	0	0	....	1.20	14.8	0.09	140	234	130	3283	141	
19–20	1333	....	....	....	0	0	....	1.94	25.9	....	112	226	148	3168	141	
20–21	1348	14.29	1.91	11.1	0	0	....	1.71	23.0	0.08	147	235	270	3896	143	Glucose 150 gm. (50 gm. with each meal).
21–22	1670	15.53	1.31	7.0	0	0	....	1.63	27.3	....	123	155	99	2352	143	
22–23	1770	13.26	1.14	7.1	0	0	....	0.81	14.4	....	96	130	113	2066	141	
23–24	1410	13.67	0.79	4.8	0	0	....	0.88	12.3	....	108	118	67	1815	....	
24–25	1170	12.75	0.57	3.7	0	0	....	0.98	11.5	....	124	125	60	1917	....	
25–26	2315	18.90	0.98	4.3	0	0	....	1.29	30.0	0.08	110	130	148	2267	....	Glucose 100 gm. with midday meal.

* The first three blood sugar determinations were made with a standard that evidently yielded too high results. A new and carefully controlled standard in the subsequent determinations invariably gave lower readings, even after the administration of dextrose.

† Legal's reaction for acetone and Gerhardt's ferric chloride test for diacetic acid were used, + indicates a trace, ++++ a maximal reaction.

‡ No alcohol was given at any time.

TABLE 2. BLOOD SUGAR DETERMINATIONS AND DEGREE OF GLYCOSURIA AFTER A MEAL CONTAINING 100 GRAMS OF DEXTROSE.

OCTOBER 25. A MEAL CONTAINING 100 GRAMS DEXTROSE.

	Before the Meal.	After the Meal.				
		35 min.	1 hr. 10 min.	1 hr. 35 min.	2 hrs. 5 min.	2 hrs. 40 min.	3 hrs. 15 min.
Blood Sugar, per cent	0.09	0.15	0.12	0.12	0.09	0.07	0.06
Urine Glucose, per cent	....	....	1.0	....	....	....	0.6

TABLE 3. HOURLY GLUCOSE EXCRETIONS AND THEIR RELATIONS TO DIET AND BLOOD SUGAR.

Date.		Time.	Urine. cc.	Glucose. Per cent.	Glucose. Total gm.	Glucose. Gm. per hour.	Blood sugar. Time.	Blood sugar. Per cent.	Diet. Time.	Protein, gm.	Fat, gm.	Carbohydrate, gm.
Oct. 13–14	Day.	8–10	845	0.16	1.4	0.7	....	....	6	13	21	3
		10–12	370	0.14	0.5	0.3	....	....	10	12	7	1
		12– 2	265	0.24	0.6	0.3	....	....	12	33	8	6
		2– 4	275	0.16	0.4	0.2	....	....	..	..	..	..
		4– 6	168	0.38	0.6	0.3	....	....	5	20	18	5
		6– 8	130	0.59	0.8	0.4	....	....	..	..	..	..
	Night.	8– 8	325	0.64	2.1	0.2	....	....	..	..	..	..
Oct. 15–16	Day.	6– 8	133	0.69	0.9	0.5	....	....	6	29	55	6
		8–10	220	0.79	1.8	0.9	9	0.09	..	..	..	..
		10–12	164	0.49	0.8	0.4	....	....	10	12	6	1
		12– 2	213	0.66	1.4	0.7	....	....	12	51	31	7
		2– 4	128	1.08	1.4	0.7	....	....	..	..	..	..
		4– 6	97	1.50	1.5	0.8	4	0.09	5	35	42	14
		6– 8	131	1.20	1.6	0.8	....	....	..	..	..	..
	Night.	8– 6	410	1.25	5.2	0.5	....	....	..	..	..	..
Oct. 16–17	Day.	6– 8	82	0.84	0.7	0.4	....	....	6	31	60	31
		8–10	170	1.09	1.8	0.9	9	0.09	..	..	..	..
		10–12	246	0.72	1.8	0.9	....	....	10	2	1	0
		12– 2	290	1.08	3.1	1.6	....	....	12	75	42	33
		2– 4	144	1.35	2.0	1.0	....	....	..	..	..	..
		4– 6	110	1.66	1.8	0.9	....	....	5	36	42	30
		6– 8	34	2.22	0.8	0.4	....	....	..	..	..	..
	Night.	8– 6	197	2.38	4.7	0.5	....	....	..	..	..	..
Oct. 19–20	Day.	6– 8	102	1.96	2.0	1.0	....	....	6	39	82	61
		8–10	116	1.78	2.0	1.0	....	....	..	..	..	..
		10–12	108	1.51	1.6	0.8	....	....	10	2	0	0
		12– 2	196	1.76	3.4	1.7	....	....	12	25	72	55
		2– 4	170	1.61	2.7	1.4	....	....	..	..	..	..
		4– 6	98	2.08	2.0	1.0	....	....	5	46	72	32
		6– 8	88	2.94	2.5	1.3	....	....	..	..	..	..
	Night.	8– 6	455	2.18	9.9	1.0	....	....	..	..	..	..
Oct. 20–21	Day.	6– 8	122	2.3	2.8	1.4	5.50	0.08	6	36	78	*95
		8–10	132	1.2	1.6	0.8	9	0.08	..	..	..	..
		10–12	136	1.6	2.2	1.1	....	....	10	2	0	0
		12– 2	176	2.3	4.0	2.0	1	0.11	12	64	71	*90
		2– 4	114	1.8	2.0	1.0	....	....	..	..	..	..
		4– 6	172	1.3	2.2	1.1	....	....	5	45	86	*85
		6– 8	106	2.2	2.3	1.2	7	0.08	..	..	..	..
	Night.	8– 8	390	1.5	5.9	0.5	....	....	..	..	..	..
Oct. 21–22	Day.	8–10	280	1.92	5.4	2.7	....	....	6	33	71	29
		10–12	245	1.25	3.1	1.6	....	....	..	..	..	..
		12– 2	255	1.56	4.0	2.0	....	....	10	5	0	1
		2– 4	190	1.52	2.9	1.5	....	....	12	58	43	24
		4– 6	160	1.64	2.7	1.4	....	....	..	..	..	..
		6– 8	140	2.27	3.2	1.6	....	....	5	27	41	45
	Night.	8– 8	400	1.54	6.2	0.5	....	....	..	..	..	..

* 50 gm. carbohydrate given as dextrose.

grams of calcium chloride by mouth on October 26, and 24 gm. on October 27 and on October 28, had no effect in reducing the sugar output. Further experiments in this direction were contemplated but could not be carried out because of the limited stay of the patient in the hospital.

SUMMARY.

From these studies it becomes apparent that this patient showed glycosuria, but none of the other abnormalities characteristic of an impaired carbohydrate metabolism. This case, therefore, may be added to the small list of those that point to the existence of a so-called renal diabetes or renal glycosuria. The slightly diminished phenolsulphonephthalein excretion, the slight elevation of Ambard's constant above the normal, as well as the glycosuria, point to a depressed kidney function. The absence of any further subjective or objective signs, past or present, leads to the conclusion that a renal glycosuria is an interesting anomaly, but of no importance to the organism as a whole.

The question of prognosis in this condition is the most important problem which remains to be solved. It is well known that instances of true diabetes may persist for years without changing from a mild to a severe type in spite of the lack of any systematic efforts at dietary restriction, thus resembling renal glycosuria. It is not certain that what is termed renal diabetes may not develop into diabetes mellitus, especially since comparatively little is known of the early stages of true diabetes. The number of cases of renal glycosuria thus far observed has been small and none of them has been followed for a sufficient length of time to ascertain whether renal diabetes is congenital, and not an acquired anomaly, and whether it may persist indefinitely without changing its characteristics.

The intensity of renal glycosuria should vary with the degree of kidney permeability to dextrose. With a threshold only slightly depressed, an intermittent glycosuria often of an apparently unexplained origin may be present; with a very marked depression, changes approximating the conditions found in phlorhizin poisoning should develop. Intermediary degrees of kidney involvement should have glycosurias of corresponding intensity. If the present ideas of the relations of a diminished kidney threshold for sugar are true, all the grades of intensity indicated should be demonstrated in the course of time.

BILATERAL AND COMPLETE TRIGEMINAL PARALYSIS WITHOUT INVOLVEMENT OF OTHER CRANIAL NERVES.*

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The anatomical relations of the trigeminal nerve as it emerges from the pons, its short intracranial course, and the protected position of its ganglion within the dural sheath suggest a probable explanation for the frequency with which this nerve escapes in diseases of the cerebral meninges.

Different opinions have been expressed, however, concerning the incidence of syphilitic affections of the fifth nerve, and Uhthoff [1] claims that this nerve is involved in 14 per cent of all cases of cerebral syphilis. Forster [2] states that neuralgic disturbances are not uncommon, and that motor and sensory paralyses have been observed. Oppenheim [3] has also seen involvement of the motor root in one case, and von Ziemssen [4] records a case with sensory changes, implication of other cranial nerves, and motor paralysis. In Lowenfeld's [5] case, there was sudden isolated paralysis of the muscles of mastication upon one side, and Nonne [6] has frequently observed syphilitic trigeminal affections, but usually in association with other cranial nerve symptoms. Hutchinson [7] makes the surprising statement that he has "scarcely seen paralysis of the fifth nerve except as the result of syphilis"; and, although only one fifth nerve is affected, "it shows no tendency to become complicated by involvement of other cranial nerves." He has, however, observed two cases in which both trigeminal nerves were affected.

Unilateral motor paralysis has been observed in two cases by Spiller and Camp.[8] Sensory changes in the trigeminal area were not present, but in one case associated hemiparesis and bilateral oculomotor paralysis were noted. In the second case, fibrillary tremor of the right masseter muscle had been noted and there was a history of pain in the right trigeminal area; but the patient's condition was such that a satisfactory sensory examination could not be made. Other cranial nerves were not involved, but there was a recent right hemiplegia discovered at autopsy to be due to meningitis and temporal lobe softening, and the pontile and spinal tracts of the fifth nerve were degenerated.

Although various combinations of symptoms have been described in syphilitic affections of the trigeminal nerve, there are certain features of the disease which are more or less characteristic: The more common symptoms are confined to sensory disturbances in one or two branches of the nerve, and rarely involve all three branches; the affection is almost always unilateral and associated with implication of other cranial nerves; the motor fibers are rarely affected; complete motor and sensory paralysis is rare even when other nerves are involved, and extremely rare as an isolated paralysis; and lastly, the disease is sometimes bilateral.

Complete syphilitic paralysis of the fifth nerve has been described by Neiding [9] who refers to a similar observation by Kuttner. In Neiding's case, the symptoms, which were con-

* Read before the Philadelphia Neurological Society, February 25; and before the Baltimore Neurological Society, March 17, 1916.

fined to the right trigeminal area, were attributed to syphilitic disease of the Gasserian ganglion. Other cranial nerves were not affected and there was no evidence of involvement of the central nervous system. Complete insensibility and motor paralysis were present upon the affected side, and taste was lost upon the anterior portion of the tongue. Examination of the blood showed a strongly positive Wassermann reaction, but a study of the spinal fluid was not made. After three months of active specific treatment there was marked improvement and the patient was considered clinically well.

Total syphilitic paralysis of the trigeminal nerve, either alone or in combination with other cranial nerves, is of sufficient importance to make even a clinical record of such cases valuable; and the peculiar syndrome observed in the patient whose illness is related in this paper is, I believe, unique in medical literature.

F. M., a male, unmarried, aged 29, who complained of "syphilis," was admitted to the service of Dr. H. H. Young at the Johns Hopkins Hospital, January 19, 1915. The family history is unimportant, and there is a personal history of the usual diseases of childhood, several attacks of malaria, and at the age of 19 gonorrhœa complicated by a double epididymitis. Six weeks ago, December 4, 1914, he noticed a sore upon the left side of the foreskin which was diagnosticated as a chancre, but for which he received only local treatment from his family physician. The primary lesion healed, and the patient considered himself well until January 9, 1915, when he began to complain of severe headaches, sore throat and a profuse skin eruption.

Examination upon admission to the hospital shows the presence of a hard chancre on the foreskin slightly to the left of the median line. Its center is covered by a small scab, beyond the edges of which there is an indurated area, measuring 1 x 2 cm. The inguinal glands are indurated and enlarged, and over the trunk and forearms there is a maculo-papular eruption.

Salvarsan, 0.6 gm., was administered intravenously, January 19, 1915; it was followed by a somewhat severe constitutional reaction. A second dose, of 0.6 gm., was administered January 26, to which he reacted only slightly. Business affairs called the patient away from Baltimore, and on February 2, without receiving further injections of salvarsan, he left for Porto Rico, with directions for taking "mixed treatment" by the mouth. The treatment was faithfully adhered to during his absence, until the following symptoms made their appearance.

Upon returning from a long automobile ride, March 8, 1915, three months after the primary lesion, he complained of ringing in both ears and severe headache. The next morning these symptoms had subsided, but after another long drive he went to bed because of a return of the intense headache associated with a chill, fever, nausea and vomiting. He was treated for "la grippe" for three or four days, after which all of the symptoms disappeared except the headache, which persisted and gradually became more intense; there was also a severe pain in the left side of the face "resembling facial neuralgia."

These neuralgic attacks continued until about March 14, when the patient noticed that the entire left side of the face felt numb, and chewing upon this side was difficult. Numbness in this region was so pronounced that movements were not fully appreciated, and he felt, when smiling, as if the face were drawn to the right side; but when this act was performed before a mirror he could notice no difference in the movements of the two sides of the face. Six days later, March 20, the right side of the face became slightly numb, without, however, any preceding pain, and it was almost impossible to masticate anything solid. Within two days the condition had so progressed that the entire front of the head and both sides of the face were completely numb, and it was impossible to chew or even close the jaws. There has been no difficulty in the movements of the eyes or lids, nor is there a history of diplopia. Taste, swallowing, speech and movements of the tongue have not been impaired, and control of the arms, legs and sphincters has not been disturbed.

The patient became alarmed about his condition and decided to return to Baltimore, where he arrived March 30, and was admitted for the second time to the service of Dr. Young, who, on April 3, asked me to see the patient, when the above history was obtained. At this visit it was also learned that headache, nausea and vomiting, which had been prominent symptoms during the journey to Baltimore, since admission, had been less frequent; but that within the past two days he had experienced severe pain in the right thigh and difficulty in moving the right foot.

Physical examination by Dr. Cameron reveals no abnormality in the thorax or abdomen, and a laboratory report upon the blood and urine states that in the former there is a leucocyte count of 13,600, and that in the latter sugar and albumin are not detected. Since admission the temperature has varied from 99 to 101.4° F.

Examination of the nervous system is as follows: The patient is lying in bed with the mouth partly open, and is unable to close it when requested to do so. He looks ill, and complains of headache and pain in the face.

There are no subjective disturbances of the olfactory nerve, and when tests are made with valerian and oil of cloves, these substances are correctly named.

There is no disturbance of vision and the optic disc in each eye is of good color, the margins are well defined, the veins are not engorged, and the lamina cribrosa is visible.

Both pupils are slightly dilated, but equally so, and respond promptly to light, directly and consensually, and during accommodation. The extrinsic ocular muscles act normally in all movements of the eyes, and there is no nystagmus or strabismus. The left upper lid shows slight ptosis and there is consequent narrowing of the left palpebral aperture. It is stated, however, that this condition has existed since birth, and that it has not increased since the onset of the present illness. Movement of the upper lid is unimpaired.

The Fifth Nerve.—The patient complains of almost constant headache, pain in both ears, and numbness of the entire face. Objectively, there is complete loss of tactile, thermic and pain sense in the entire sensory area of both trigeminal nerves, except that in the distribution of the left maxillary nerve a pinpoint is occasionally recognized as such, although it does not produce a sensation of pain. Corneal sensibility is completely lost upon both sides, and when the eyes are closed, irritation of the nasal and buccal mucous membranes produces no response from either side, nor is the patient cognizant of what is being done. All forms of sensibility, except deep pressure, are lost upon both sides of the tongue in its anterior portion.

The motor portion of each fifth nerve is completely paralyzed and the lower jaw hangs drooping from its articulation, and cannot be closed voluntarily or moved in either lateral direction (Fig. 1). Tremor of the temporal and masseter muscles is not observed, but these muscles, upon both sides, fail to respond to faradic stimulation, and their reaction to the galvanic current is slow and lazy.

At rest the face is symmetrical and the naso-labial folds are of about equal intensity. In wrinkling of the brow, frowning, closing the eyes, and showing the teeth, the movements are equally well performed upon the two sides (Fig. 2). Taste, when tested with solutions of sugar, salt, acetic acid, and quinine, shows no impairment upon either side of the tongue, anteriorly or posteriorly.

A watch is heard slightly better with the right than with the left ear; and, because of this auditory defect, the patient was later referred to Dr. Jas. Bordley, who examined the ears and reported

that moist eczema was present in both external auditory canals. The vestibular portion of the eighth nerve was not examined minutely, but there were no definite subjective or objective evidences of disturbance in this division of the nerve.

There has been no difficulty with speech or in swallowing except that due to inability to move the lower jaw; and fluids do not regurgitate. The soft palate, although insensitive upon its oral surface, moves equally well on the two sides when saying "Ah," and the palatine muscles respond promptly to faradic and galvanic stimulation. The sternomastoid muscles and the trapezeii function normally and show no weakness or atrophy upon either side.

The tongue is protruded promptly and in the median line. It is slightly tremulous, but is under good control; the motor power is not diminished, and the response to both forms of electrical stimulation is prompt and vigorous.

A jaw-jerk is not obtained. The biceps and triceps tendon jerks are easily obtained and are equally active upon the two sides. Both knee-jerks are slightly hyperactive, and the left is greater than the right. The tendon Achillis jerks are present, but this reflex is more active at the right ankle. There is no ankle or patellar clonus. The epigastric, abdominal and cremasteric reflexes are equally active upon the two sides. Plantar stimulation and decending tibial irritation produce plantar flexion of the great toe upon each side.

There is no evidence of ataxia, weakness, or loss of voluntary control in either upper extremity, and sensation in the arms is normal. When standing with the feet together and the eyes closed, there is some unsteadiness; but the heel-tibial test is accurately performed with either leg. Walking is slightly impaired because of pain in the right leg and difficulty in flexing the right foot, which gives the characteristic "steppage" quality to the gait. Motor power in both legs is well preserved, except that upon the right side there is weakness in the tibial and peroneal group of muscles, and these muscles show diminished excitability to both forms of electrical stimulation and respond slowly to the galvanic current. Deep pressure over the right peroneal nerve is definitely painful, and there is moderate diminution of cutaneous sensibility in the area innervated by this nerve. Sensory changes other than those already noted in connection with the head and outer portion of the right leg are not detected.

Lumbar puncture.—March 31. The spinal fluid is slightly cloudy and under increased pressure. Cell count, 740 per cu. mm. A stained smear shows that the majority of these cells are lymphocytes, but a few polymorphonuclear and epithelial cells are observed. The globulin is greatly increased, and the Wassermann test is strongly positive. Serum Wassermann, positive. (Dr. Cameron.)

A clinical diagnosis of syphilitic meningitis with bilateral involvement of the trigeminal nerve, and syphilitic peroneal neuritis was made.

Treatment and Subsequent Course.—April 3. Salvarsan, 0.4 gm., was administered intravenously. The reaction was moderate.

April 5. The headache is less intense and the patient is generally more comfortable. There is no involvement of other cranial nerves, and the neurological examination is the same as at the first visit. Mercurialized serum (Hydrarg. bichlorid. gr. 1/25) administered intradurally. An examination of the spinal fluid at the time of administration is as follows: Fluid, slightly cloudy; pressure 220 mm.; cell count, 510 lymphocytes; globulin increased; a Wassermann test was not made. Reaction to the treatment was moderate. The temperature did not rise above 99.6° F., there was some pain in the legs for 24 hours, but no nausea or vomiting.

April 10. General condition much improved. The headache and pain in the face almost entirely absent. Salvarsan, 0.6 gm., administered intravenously. Reaction moderate.

April 12. General condition improved. No involvement of other cranial nerves. Neurological symptoms unchanged. Mercurialized serum (Hydrarg. bichlorid. gr. 1/25), administered intradurally. Spinal fluid examination: Fluid clear; pressure 220 mm.; cell count 165; globulin increased; Wassermann, not made. Reaction similar to that following the first treatment, except that the temperature rose to 101.4° F.

April 17. Salvarsan, 0.6 gm., administered intravenously. Reaction moderate. The patient was discharged from the hospital two days later, with instructions for stimulating, electrically, the paralyzed muscles, and the request to return at intervals for further treatment. Examination at this time shows that the neurological condition is unchanged. The headache and pain in the face have entirely disappeared, but there is still complete sensory and motor paralysis of both fifth nerves and right foot-drop.

April 20. Admitted to the Church Home and Infirmary for further treatment. Examination to-day shows a very slight return of sensation in each mandibular and lingual division of the trigeminal nerves, but the entire area supplied by the two upper branches of each fifth nerve is still completely anæsthetic. Mercurialized serum (Hydrarg. bichlorid. gr. 1/25), administered intradurally. Spinal fluid examination: Fluid clear; pressure 190 mm.; cell count 70; globulin, trace; Wassermann test, not made. The treatment was followed by a rise of temperature to 101° F., intense pain in the legs and slight headache.

April 21. The corneal reflex in each eye is absent, but the patient says he can feel the cotton when it is drawn across the cornea.

April 26 and May 3. Salvarsan, 0.6 gm., administered intravenously.

May 4. Examination to-day shows that there is still complete insensibility in the ophthalmic division of each trigeminal nerve, and the corneal reflex is absent in each eye; but there is a slight return of sensation in the maxillary and mandibular distribution upon both sides, although portions of these areas are still comparatively anæsthetic. The lower jaw can now be moved so that approximation of the teeth is possible. Because of the marked reaction following the previous intradural treatment, and the definite improvement in symptoms, it seems advisable to discontinue radical treatment for a while, and mercurial inunctions are ordered.

May 26. The patient's general condition shows marked improvement, and he states that he can now feel drafts of air upon the face, or in the nostrils when respired, and that he knows when he has his hat on. There is still pronounced weakness of the muscles of mastication, and objects cannot be held between the teeth, although the upper and lower jaws can be approximated. Bilateral corneal anæsthesia persists, and sensibility in the distribution of both maxillary and supraorbital nerves is still greatly impaired; but in each mandibular area sensation is practically normal. The right foot-drop is still present.

May 28. Lumbar puncture and intradural administration of mercurialized serum (Hydrarg. bichlorid. gr. 1/25). To these he reacted only slightly. Spinal fluid examination at this time: Fluid clear; pressure 240; cell count 8; globulin, faint trace; Wassermann negative; serum Wassermann negative.

The following day the patient was discharged from the hospital, and it became necessary for him to leave Baltimore two weeks later, without having received further treatment except the continuation of mercurial inunctions. In the course of eight weeks, then, five doses of salvarsan intravenously, alternating with four doses of mercurialized serum intradurally, were administered at the intervals recorded in the hospital notes.

A letter from the patient dated November 26, 1915, states: "My health has been splendid. My foot is normal again and my jaws allow me to eat everything now. The left side, which as you know, was hit hardest, is still without the fleshy muscle. My eyes, nose and upper lip are still very numb."

FIG. 1.—Photograph of the patient, April 5, 1915, showing complete jaw-drop from bilateral fifth nerve paralysis.

FIG. 2.—Photograph of the patient, April 5, 1915, showing his ability to perform ordinary facial movements. The lips cannot be closed completely because of immobility of the lower jaw.

Complete motor and sensory paralysis of both fifth nerves, without implication of other cranial nerves has, I believe, not been previously recorded in medical literature. It is true Hutchinson, Leudet, and Uhthoff have reported instances in which both nerves were involved, but an analysis of their cases shows that the affection was quite different from that which I have just described.

In Hutchinson's cases, the two nerves were not simultaneously affected, and he does not state to what extent they were involved, or whether there was implication of other cranial nerves. Leudet's [10] patient, when first examined, showed disturbance of vision, ptosis, strabismus in the left eye, muscular disorders of the right eye, and anæsthesia in the entire distribution of the left trigeminal nerve. He was seen at intervals during a period of four years, after which, at the final observation, it was noted that the condition upon the left side of the face had remained practically unchanged: that, in addition, the right eye was totally blind and the entire right side of the face was anæsthetic. No note was made upon the condition of the motor portion of either fifth nerve. An autopsy was secured and it was found that the left Gasserian ganglion, which was pale, contracted, and reduced in size, had been invaded by an exostosis of the temporal bone.

Seventeen years later Labarrière [11] refers to a case of syphilitic involvement of both trigeminal nerves, which, by some students of the subject, appears to be regarded as an additional instance of the affection, but the case in question, No. 13 in Labarrière's studies, is identical with one described by Leudet, to whom full credit is given in the author's thesis.

Although it is impossible, without anatomical evidence, to determine the exact character and location of the lesion in my case, the syphilitic nature of the affection is evident. Hæmorrhage into, or acute inflammation of both trigeminal nuclei would, of course, produce bilateral fifth nerve paralysis; but the subacute onset of the disease does not suggest hæmorrhage, and it is improbable that a pontile lesion of this extent could occur without neighborhood symptoms, or even a fatal termination.

That intense meningitis was present is indicated by the unusually high cell count in the spinal fluid; but it is unusual to witness this degree of meningitis without implication of other cranial nerves. Bilateral syphilitic ganglionitis suggests a probable explanation, but such a condition, if confined within the dural covering of the ganglia, makes it difficult to explain the marked lymphocytosis in the spinal fluid. Diffuse meningeal inflammation upon the surface of the pons might involve the trigeminal roots upon each side, and account for the cytological changes in the spinal fluid. It is not probable, however, that the sixth nerves would have escaped in such a lesion. Local meningitis upon each lateral aspect of the pons, but not extending across the mid-line, might produce bilateral trigeminal radiculitis and resulting paralysis of both nerves, without implicating the sixth nerve, or those lateral to the fifth nerve. Such a lesion would account for the lymphocytosis and at the same time explain the long duration, and perhaps permanency of some of the symptoms, from central degeneration of the sensory fibers. While it may be difficult to locate, exactly, the lesion in this case, there is little doubt that the symptoms were due to intracranial involvement of both fifth nerves.

There are two important clinical features which deserve especial emphasis. Trophic disorders following lesions of sensory ganglia are not infreqently observed, and it is not improbable that the bilateral auricular eczema may have been of this origin. In Neiding's case, furunculosis of the nasal cavity upon the affected side was attributed to the same cause.

According to Nonne, Rumpf has been unable to find in the literature a single instance of syphilitic disease of the fifth nerve in which taste was lost. This statement is, however, contradicted by Neiding, in whose patient taste was lost upon the anterior two-thirds of the affected half of the tongue. In view of Rumpf's studies and the preservation of taste in the case which I have studied, it appears that the centripetal fibers conducting this special sense do not enter the central nervous system by way of the Gasserian ganglion. It is not improbable that the loss of taste in Neiding's case may be explained by an extension of the inflammatory process into the trunk of the mandibular nerve with involvement of the incorporated fibers of the chorda tympani.

It is a pleasure to acknowledge my indebtedness to Dr. Hugh H. Young for referring the patient to me, and for the privilege of conducting this study in the Brady Urological Institute.

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DIGESTION: AN HISTORICAL SURVEY.

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Any survey of the views that have been held by mankind in the past on the subject of animal digestion and bodily nutrition must necessarily be synchronous with the history of medical science.

The majority of ancient medical records that have come down to us are largely occupied with references to diet and descriptions of imaginary causes of ill-health. In the absence of direct testimony as to the conception held by the ancients with regard to the manner in which the food they ate nourished their bodies, we are forced to rely upon statements throwing a side-light on the general subject.

The ancient Egyptians held the belief that food was the chief source of disease, and they followed precept by practice in taking a purgative and an emetic three times a month. However, there was also present in the Egyptian mind the idea that the body was ruled by demons, and that digestion was performed by the aid of a "demon" or spirit, whereas indigestion was due to the anger of the spirit.

The authors[1] of the great epic poems of the Hindus have given evidence, however, of the existence of other theories related to demonology, according to which principles or humors were supposed to reside in the body and to direct the natural digestive processes. Thus the Aryan writers recognized three principle humors: *Vata*—situated between the feet and the navel—or Wind; *Pitta*—between the navel and the heart—or Bile; *Kafa*—between the heart and the top of the head—or Phlegm.

Kafa was predominant during the period when the food was in the mouth; Pitta, during the course of digestion; and Vata, after the food in the stomach was fully digested. If from any cause any one of these principles became unduly prominent, the condition of the bowels was affected. Thus, when Vata exercised too strong an influence, the bowels were costive; when Pitta, or the bile, was in the ascendant, they were loose; whereas they acted normally when Kafa was the most powerful.

These writers also describe a *Pachaka*, or fire of digestion, situated between the stomach and the small intestine, which assisted digestion and imparted heat to the body. Pachaka was also able to separate the nourishing portions of the food from the dejecta.[2]

Among the Chinese the medicine and physiology of yesterday are the same as that of to-day. They and their civilization, like mountains, have attained a certain limited height, have existed there, inflexible and almost unchanged, for thousands of years. Physiology occupies the lowest grade in Chinese medical science and nothing of value or interest relating to the subject of digestion is to be found in their medical literature.

Among the ancient Chaldeans, Babylonians and Persians we find that medicine probably presented the lowest form that has ever existed in civilized communities. The Chaldeans appear to have contributed absolutely nothing to the general stock of medical knowledge.

The medicine of the Medes and Persians resembled somewhat that of the Chaldeans, but had a still closer analogy to that of the Hindus, with the important difference that it produced no Susruta or Charaka.

Turning our attention to early Greece, we find that their philosophy exercised so essential an influence upon their medicine that the fundamental doctrines of the former formed the theoretical principles of the latter, and we cannot well keep the two separate. In fact, the whole medicine of the Greeks bears the special character of a philosophical science, if we except that of Hippocrates alone.

Nevertheless, from quite an early period, the medical writers of the ancients recognized that the stomach was one of the chief organs concerned in digestion and they paid considerable attention to it. According to these Grecian natural philosophers, the food, after it was taken into the stomach, putrified or was cooked. Anaxagoras (500-428 B. C.), a member of the Ionic school (600 B. C.) and teacher of Pericles, imagined that the animal body, by means of a kind of affinity, appropriated to itself from the nutritive supply the portion similar to itself. His philosophical influence was great, but a more important influence, especially later, was exercised by Empedocles (504-443 B. C.), whose assumption of the four elements—water, air, fire, and earth—formed a foundation stone for the doctrines of Hippocrates II of Cos, justly named the Father of Medicine.

It is not within the province of this paper to extol or to magnify the achievements or failures of medical celebrities, except in so far as they may be related to the historical development of our knowledge of digestion. Hippocrates taught that gastric digestion was brought about by a sort of internal cooking or coction—"pepsis" (digestion)—possibly through the agency of the "innate heat"[3] of the body. The views of the Hippocratists were based upon the assumption of the four elements of Empedocles—fire, water, earth and air—whose mixture and cardinal properties (warmth or heat, coldness, moisture and dryness) formed the body with its constituents. To these corresponded the cardinal fluids, blood, phlegm, black and yellow bile, in the order mentioned. The heat or warmth from the blood caused digestion of food. The liver formed blood and bile and assisted the process of coction in the stomach by increasing its heat. To certain foods were ascribed qualities corresponding to the four humors, and such foods were recommended for maladies due to excess or defect of the humors. Thus to Hippocrates and his followers we owe the

[1] See Jee: History of Aryan Medical Science, London, 1896.

[2] By some this body was looked upon as being identical with Pitta, or bile. The author of the "Rasa-pradipa" imagined it to be a minute heating substance situated in the centre of the navel.

[3] Callidum innatum, the "animal heat" of later physiologists. (See Harvey.)

foundation of a science of dietetics. But about their ideas on the physiology of digestion nothing further need be said.

Next there appeared the philosophy of Plato (427-347 B. C.), which, paying slight respect to all facts and holding all observation by the senses as deceptive, won a controlling influence over medicine. Plato, though the noblest of philosophers, has hardly deserved well of the profession of medicine. As so often happens, the enunciation of a rational doctrine by Hippocrates tended to cause a reaction, and men now began to seek to deduce the underlying principles of physiology and disease, not from the study of facts, nor from the evidence of the senses, but from purely mental speculations. Reflection ranked higher than experience. The hold which this method of solving physiological problems obtained on the physicians and thinkers of that time retarded the advance of physiological knowledge by a period only to be reckoned by centuries. Plato, for instance, gravely propounded the theory that some of the fluid drunk passed through the wind-pipe into the lungs, and there served to cool the heart; the liver served the lower desires; the spleen furnished an abode for the impurities of the blood. The intestine was long and tortuous, in order that the food need not be renewed so often and thus disturb the contemplations of the mind.

Aristotle (384-321 B. C.), the teacher of Alexander the Great, exercised no such important and immediate influence upon the views of ancient medicine as did Plato. He did not, like Plato, call about him a numerous school of followers; nevertheless, his great mind supplied for centuries the principles of thought and observation, and the material for the extension of all branches of knowledge, but especially of the natural sciences, of which he is considered the creator. He did much to break down the excessive idealism current in the system of Plato, and to bring thought back into more realistic grooves. Like the Father of Medicine, he looked upon digestion as brought about by a process of coction in the stomach, the resulting chyle proceeding to the heart. He looked upon the blood as the medium by which the nutritive material for the growth and warming of the body was conveyed through the vessels. Bile he regarded as a useless excrementitious product.

The school of Alexandria, founded by Herophilus and Erasistratus (about 330-280 B. C.) covered a period, which when compared with the preceding dogmatic tendency of medicine, must be regarded as an epoch of realism.[1] It was distinguished by the appearance of the famous founder of human anatomy, Herophilus of Chalcedon, and of Erasistratus of Inlis, a physician valued no less highly than his contemporary. They, however, differed widely in their tenets.

Herophilus possibly discovered the chyliferous and lymphatic vessels, and the duodenum, which he named; he also described the liver quite accurately. He was a follower of Hippocrates and of the humoral doctrine. Erasistratus, however, discarded the humoral system, and propounded one of his own, based upon the theory that the arterial vessels and heart contained "vital spirits" (pneumata). He ascribed digestion to the result of trituration of the food between the stomach walls (Iatrophysician!), nutrition to the addition of new particles, and secretion to the action of what he termed the non-attractive force. He thought that the bile was useless, the spleen superfluous, and showed that fluids did not enter the air passages.

Few records have come down to us of the medical opinions current among the inhabitants of early Rome, but in so far as we can speak of such an art, it did not rise above the very first rudiments. Gradually with the advent of Grecian medical influence some advancement was made.

At a much later time (200-131 A. D.) flourished the most famous of all the Roman physicians, Claudius Galen, of Pergamus. He was a man who not only knew all there was to know in his age, but who also possessed sufficient talent and originality to acquire the position of a medical dictator, and to maintain it for more than a thousand years. His physiology, though somewhat marred by excessive theorizing, was admirable. Following Hippocrates and the Alexandrians, he emphasized the great importance of the study of anatomy and physiology, and performed many experiments in both of these sciences.

Galen believed that the food, after it reached the stomach, was digested by the process of "coction"; the results of digestion were then carried to the liver by the portal vein, where they were transformed into blood (an important error which was not discarded until the 17th Century). This blood, now called "natural spirits," was then carried to the heart where by the aid of the innate heat of this organ, it was laden with "vital spirits." The heart then drove into the lungs, through the pulmonary artery, as much of the blood as was required for their nutrition. At the same time the remainder of the blood was driven through the veins to all parts of the body, supplying its various portions with nutriment. Galen, therefore, considered the venous portion of the circulation as the seat of nutrition. The arterial blood (blood laden with vital spirits), upon reaching the brain, there generated the "animal spirits."

Little of interest or of value can be gathered from the writings of those who followed Galen. For a period to be measured only by centuries the current opinions were only variants of Galen's views. In the dark ages of Medieval Europe the tendency of all knowledge was to recede rather than to advance; indeed, the influence of Christianity tended to hasten the decline of medicine instead of advancing its progress.

The standard of Arabic medicine, it is true, was at its highest development from the 8th to the 10th Century, but it offers us little or nothing in the way of advancement in physiological knowledge.

Early in the history of the Middle Ages, we find medicine and religion more or less firmly united together, and, from the 6th Century onward, everything medical gradually fell into the hands of the Church, and especially of the monks, whose ignorance of medical science is only too well known to medical historians. The authority of the Church in all branches of knowledge soon became paramount, and for many centuries it controlled more or less absolutely the gates of learning. The search for truth ceased to be the study of natural phenomena

[1] Called by Baas, without much error—"The epoch of antique scientific, or exact, medicine."

and the search for the reason why; it narrowed itself down to asking, "What does the Church say about it?" Truth and science came to mean simply that which was written, and inquiry became mere interpretation.

However, with the dawn of the Renaissance, the various medical sciences—anatomy, physiology and chemistry—again began to develop and the writings and teachings of such men as Vesalius (1514-1564), Servetus (1509-1553), Paracelsus (1493-1541), and Borelli (1608-1679), were in part the instruments which served to shatter to pieces the idol of authority, which was never to be put together again.

Vesalius contributed little or nothing, directly, to the science of physiology, but by his anatomical dissections he paved the way for many future physiological discoveries; and in truth we may look upon him not only as the founder of modern anatomy, but also as the distant forerunner of the English physiologist, William Harvey (1578-1667), whose discovery of the circulation of the blood opened up the avenues for scientific physiological and chemical research which has given so many glorious discoveries to the world.

Paracelsus exerted a great influence upon the development of medicine, especially chemical physiology, through his teachings in mystic alchemy, so that by some historians he is called the founder of chemical physiology.

Borelli, likewise, by his numerous experiments and discoveries in the new and infant science of physics, of which he was the real founder, hastened the development of physiological knowledge.

The 17th Century saw the birth of two distinct sciences—physics and chemistry—the latter emerging from a mystic alchemy. It was not long before they were pressed into the science of physiology, sometimes unwisely, whereby the school of physiology proper was split up into the school of those who would explain all the phenomena of the body on physical and mathematical principles, the *iatro-mathematical* or *iatro-physical* school, and into the school of those who proposed to explain all the same phenomena as mere chemical events, the *iatro-chemical* school.

In the study of the historical development of our knowledge of digestion, it is necessary to inquire into the manner in which chemistry came to the aid of those who were studying the problems of life, and thus gave rise to the chemical physiology which we know to-day.

Among the medical celebrities whose influence in the advancement of chemical physiology was paramount, the names of the chemical mystics, Basil Valentine (1450-?),[5] Paracelsus or Theophrastus Bombast von Hohenheim,[6] and van Helmont must be considered first of all.

Basil Valentine is generally credited with the conception of the three "elements," replacing the old idea of the ancients of the four elements—earth, air, fire and water. He designated these three elements, sulphur, that which is combustible; mercury, that which is volatile; and salt, that which remains after burning. To this conception of the properties of matter he added his *archæus*, or *archæi*, which were to him the spiritual forces governing and determining the phenomena of the universe, chemical changes included.

Apparently the doctrines of Basil Valentine obtained a firm hold upon the mind of Paracelsus. He greatly enlarged and developed them by the new light he had gained by his own researches, observations and studies. He was a chemist through and through, but delighted to enshroud his chemical conceptions with the veil of mysticism.

According to him, the two important facts of Nature were visible matter and invisible forces. The former consisted of the three elements—sulphur, mercury and salt, with their properties, which were capable of bringing about changes in this visible matter. The latter were spiritual forces, prominent among which were the *archæi*, to which matter was subject and by which its changes were governed. All chemical and physiological processes were governed by the *archæus*. He looked upon digestion as carried out by this presiding force or spirit within the body. Its home was in the stomach and it separated the material useful for nutrition, the "essence," from the useless, the "poison," and thus became the alchemist of the body. Digestion was to him a kind of putrefaction, by which, on the one hand, the assimilation of the nutritive slime, on the other, the formation of the excrement, was rendered possible. Health was recognized by the regular action of this *archæus;* disease, *i. e.* indigestion, was the failure of the *archæus* to govern aright.

Such conceptions as these were considered by Vesalius and his followers as the ravings of an ignorant charlatan. Nevertheless, after a lapse of nearly one hundred years they were taken up by a man, who so handled them that, in a modified and developed shape, they found lodgment in ordinary medical teachings and served as the starting point of that chemical investigation of the problems of living beings, which since that time, and especially in these later years, has been so fruitful of results. As Paracelsus, with the aid of some fifty years of increased knowledge, extended and developed Valentine's ideas, so his doctrines were in turn extended and developed with the aid of one hundred years of increased knowledge by van Helmont.

Jean Baptiste van Helmont[7] (1577-1644) is almost as strik-

[5] According to historians, Basil Valentine was probably a Benedictine monk living at Erfurt about the middle of the 15th Century. He was one of the alchemists and apparently the author of certain conceptions which played an important part in the development of chemistry and physiology.

[6] Paracelsus, born at the close of the 15th Century in Maria Einsiedeln, Switzerland, was the son of a physician and, at the age of sixteen, is said to have entered the University of Basel and soon afterwards to have studied under Bishop Trithemius at Würzburg. Later he traveled extensively and finally settled at Bâle, as a physician, in 1527. Regarding his personal history, however, there is much uncertainty. Many of his writings, discoveries, theories, and even his language, in places, are so exact reproductions of Basil Valentine's, that it is not difficult to presume that he had seen his predecessor's works in manuscript and made extensive use of them. There is also the probability that he was taught his doctrines while a pupil of Bishop Trithemius.

[7] Born at Brussels in 1577, some thirty-six years after Paracelsus' death and thirteen years after that of Vesalius.

ing a figure in medical history as Paracelsus, whom he resembled in many respects, though he surpassed him both in genius and also in learning.

In studying the writings and character of van Helmont we seem to be brought face to face with a dual personality—with two intellects of quite different kinds. There is the patient, careful and exact observer, a child of the new learning, who takes advantage of all the new discoveries and teachings; but beneath it all we can see the mystic, speculative dreamer and philosopher, weaving a fantastic scheme of the powers and forces ruling the universe, and calling in the aid of invisible supernatural agencies to explain the occurrence of natural phenomena. Throughout all his writings may be seen the continued endeavor to weave his exact chemical and physical knowledge and his spiritualistic views into a consistent whole.

Van Helmont's conceptions may be regarded as a peculiar remodeling of the pantheism of Paracelsus into a mystic and pietistic system, based upon more or less exact chemical principles. Throughout his writing we find the use of two new terms, "Blas" and "Gas." By the former he meant in all probability the *archæus* of Paracelsus; by the latter he clearly disentangles himself from all the mystic Paracelsian lore and earns for himself the title of the first of modern chemists, and at the same time the first of chemical physiologists. By "Gas" he probably meant, what we now call carbonic acid gas or carbon dioxide. "Gas" he observed to be formed in various fermentative processes by the action of a ferment, as in the making of wine or bread. He was deeply impressed with the idea of the action of ferments and makes it the basis of his system of physiology. Digestion, as well as all other changes in the body, was looked upon as a process of fermentation. And he reconciled this view with his acknowledgment of the influence of the "Blas" or *archæus* by putting forth the hypothesis that these spiritual agents worked, not by acting directly on matter, but by making use of the ferments, which were thus their servants or instruments.

The current teachings of the day regarding digestion and nutrition were in substance those of Galen. The food absorbed from the stomach and intestine was imbued with natural spirits in the liver; in the heart the natural spirits were converted into vital spirits; and in the brain the vital spirits were converted into animal spirits.

According to van Helmont this teaching was entirely wrong; instead of three there were six conversions or digestions, by which the food was transformed into the living body tissue.

To him the whole body was under the influence of an *archæus influus* or vital principle, which resided in the stomach, while every organ had its own individual *archæus insitus* directing the processes natural to it. During the process of digestion in the stomach, his so-called *first digestion*, the local *archæus* generated a ferment whereby an acid was produced to dissolve the food. This ferment, he believed, had its origin in the spleen and it was from this organ that the stomach drew all its energy. The ferment was an acid ferment, *fermentum acidum*, but the acidity was not the ferment itself, it was only the organ or instrument of the ferment.

The food, as acid chyle, then passed into the duodenum where it at once acquired a saline nature—it was the change of an acid into a salt. This duodenal change constituted his *second digestion* and was affected by a ferment furnished by the bile.[8]

The *third digestion* was that of sanguification, taking place in the mesenteric veins, liver and vena cava, and consisted in the conversion of the chyle into crude blood, brought about by the aid of another hepatic ferment.[9]

We might, with much truth, compare these three digestions with what even now-a-days we sometimes call primary and secondary digestion.

It is difficult to differentiate clearly between his *fourth* and *fifth* digestion, the former consisting primarily in the conversion in the heart of venous into arterial blood, while the latter "changes the blood of the arteries into the vital spirit of the *archæus*."

The *sixth* and last digestion took place in the kitchens of the several members, for there were as many stomachs as there were nutritive members. In this sixth digestion a spiritus, a ferment innate in each place, cooked its food for itself. "A vein," says van Helmont, meaning probably an artery, "may be considered as a vessel containing aliment prepared for the kitchens of the tissues, but it is not their kitchen. Each tissue maintains its own individual kitchen within itself." In other words, all the tissues live upon the common blood, and the power of assimilation lies in the tissue itself; it is the tissue and not the blood which primarily determines assimilation, the qualities of the blood have only an indirect influence.

Van Helmont's exposition of the mechanism of the digestive process exerted a great influence on investigators who followed him. It showed that many of the problems of the living body were chemical problems to be solved by chemical knowledge, and also a large number of the processes taking place in the living body were more or less akin to the process by which yeast produces alcohol, as in wine-making, and therefore may be spoken of as fermentations. The idea of fermentations had long been known, but its definite introduction into physiological thought is due to van Helmont.

Francois De le Boe (or Dubois), better known as Franciscus Sylvius,[10] was one of the direct successors of van Helmont in the field of chemical physiology. He was the foremost and most typical representative of the iatro-chemical school.

Van Helmont was but little influenced by the new discoveries in physiology, chemistry, anatomy and physics, whereas Sylvius was well versed in all these matters. In contrast to van Helmont, he would have nothing to do with mystic speculation about invisible agencies and spirits. He followed van Helmont, however, in considering many of the changes

[8] Van Helmont knew nothing of pancreatic digestion. Wirsung had not yet made his discovery of the pancreatic duct (1643).

[9] No mention of the lacteals is made, although he certainly must have been cognizant of Aselli's discovery in 1622.

[10] Born in Hanover in 1614; died at Leyden in 1672. He became professor of Medicine at Leyden in 1658 and for twelve years exerted a most powerful influence by his teaching.

within the body as being of the nature of fermentative processes; but to him, this fermentation was a true chemical change —an "effervescence," and he saw no reason for any additional intervention of subtle agencies, as did van Helmont.

The 17th Century was rich in new discoveries, with many of which Sylvius was by no means unacquainted. You may recall that Aselli discovered the lacteals in 1622; Harvey, the circulation of the blood in 1628; Wharton, the submaxillary duct in 1655; Stenson, the parotid duct in 1661; Wirsung, the pancreatic duct in 1642; he also appears to have observed the pancreatic juice. De Graaf made investigations on the pancreatic juice in 1664, as well as on saliva and bile. Jean Pecquet, in 1651, made known his discovery of the receptacle of the chyle and its continuation as the thoracic duct and traced it into the venous system at the junction of the jugular and subclavian veins. Two years later, 1653, Rudbeck, of the University of Upsala, described the vessels which we now call lymphatics. He saw them first in the liver and intestines and traced them to the thoracic duct, of whose existence, he says, he had become aware in 1650, before the publication of Pecquet's book. In 1673, one year after Sylvius' death, Peyer published a little tract, in which he described certain new glands of the intestines, now known as Peyer's patches. And finally, in 1682, Brunner succeeded several times in removing from a dog nearly the whole of the pancreas, and in keeping the dog alive afterwards for a considerable time. Five years later he described the glands in the duodenum, since known by his name.

Van Helmont knew nothing of either salivary or pancreatic ducts, but Sylvius with this added knowledge was led to attach the greatest possible importance to saliva; in fact, it was to him a type of the fermentative juices, and he attributed many of the changes taking place in the stomach to the saliva swallowed with the food rather than to the ferment provided by the stomach itself. The first stage of the fermentation, called chylification, was brought about chiefly through the action of this salivary secretion, according to Sylvius' view; the second stage of digestion was due to the interaction of the bile and pancreatic juice. De Graaf, his eminent pupil, had convinced himself that the pancreatic juice was of an acid nature, and this supposed truth became a foundation stone of Sylvius' views on digestion. Apparently, led away by a preconceived theory, he failed to recognize the alkalinity of the pancreatic juice and persistently insisted that it was acid, believing its use in digestion was to effervesce, to ferment, with the bile. But neither Sylvius nor his pupil seemed able to clearly explain just how it promoted digestion. De Graaf tells us that the "effervescence attenuates the viscid mucus lining the interior of the intestine, the presence of which might hinder the absorption of chyle by the lacteals; while it also assists the separation of the useful parts of the food from the useless"; but there is no explanation given how this is brought about.

According to Sylvius, in the next stage of digestion, the chyle, or the nutritious part of the food, passed into the lacteals and was conveyed through the thoracic duct into the venous system. The blood carried to the right heart by the upper great veins was chylous blood. In the right side of the heart it met with the blood of the vena cava, which he termed bilious blood, because he believed that the bile was secreted by the gall-bladder and that that part of it which was not needed in digestion was carried by the cystic duct back to the liver, where it passed into the venous system, whence, mixed with the blood, it was carried by the vena cava to the heart.

Glisson (1597-1677) and later Malpighi (1628-1694) disproved this erroneous view, but it greatly aided Sylvius in the explanation of his views of digestion and he clung to it tenaciously. According to him, the "chyle assumes the form of blood (a superficial initial change) owing to the bilious blood ascending to the heart, meeting in the right auricle and especially in the right ventricle with the lymphatic blood (of the superior vena cava) with which the chyle is mixed, and so, on account of the different or rather opposite disposition of each (kind of blood), in certain of their parts provoking an effervescence of great moment." But the "chyle reaches the ultimate perfection of blood through the continued and tempered effervescence, which by reason of the breathing of air takes place in the lungs, in the left auricle and ventricle of the heart and in the large trunks of the aorta. By the energy and help of this effervescence we think that there bursts out and springs forth the vital fire, which by rarefying the more fatty and oily parts, not only of the chyle added to the blood, but of the blood itself, and by loosely uniting together at the same time all other parts, reduces the whole into a heterogeneous, homogeneous mass and so converts the chyle into true blood."

His exposition is vague indeed, but beneath it all we can recognize his efforts to explain, in the light of added chemical knowledge, that it is unnecessary to take refuge in subtle influences and occult agencies; that all changes taking place within the body are more or less purely chemical in their nature and can readily be reproduced by experiment in the chemical laboratory.

We must at least give to Sylvius the credit of showing that there was no connection between chemistry and spiritualism; that, on the contrary, the newer chemistry in its attempt to solve vital problems was treading the path of the most naked materialism. In all probability, it was to this opening up of a line of inquiry into chemical physiology free from any taint of mysticism, that the great influence, which as a teacher he undoubtedly exercised, was largely due.

In contrast to the iatro-chemical school of which we have been speaking, there was developing during this period the so-called iatro-mathematical or mechanical school of which Giovanni Alphonso Borelli (1608-1679) of Naples was the founder, with such followers as Redi (1626-1697), the sagacious naturalist, Archibald Pitcairn (1652-1713), the British representative of the school, Lorenzo Bellini (1643-1704) of Florence, and Giorgio Baglivi (1668-1707), a pupil of Malpighi.

This school based the phenomena of digestion and other physiological processes upon the action of mechanical laws. After the manner of Erasistratus the whole process of digestion was referred to trituration by the interaction of the stomach walls.

Borelli had pointed out the great grinding, crushing force which was provided for by the muscular coats of the stomach of birds, and thought he had proved his point by feeding turkeys glass globules, hollow leaden tubes, etc., and the next day finding the leaden masses crushed and eroded and the glass pulverized. He admits that birds of prey and fishes, which are destitute of teeth and possess a membranous stomach rather than a muscular one, digest hard food in a different manner. "These animals consume flesh and bones by means of a certain very potent ferment much in the same way as corrosive liquids corrode and dissolve metals. Such a corrosive juice is poured forth by the small glands with which the membranous substance of the stomach is crowded."[11]

Archibald Pitcairn (1652-1713) like the English school generally, was far more exclusively mechanical than the Italians, and would hear nothing of acids or ferments even in digestion. "That the stomach is fully able to comminute the food may be proved by the following calculation," says Pitcairn. "Borelli estimates the power of the flexors of the thumb at 3720 pounds, their average weight being 122 grains. Now, the average weight of the stomach is 8 ounces, therefore, it can develop a force of 117,088 pounds, and this may be further assisted by the diaphragm and abdominal muscles, the power of which, estimated in the same way, equals 461,219 pounds." Well might Pitcairn add that this force is not inferior to that of any millstone!

The futility, indeed, of this mode of viewing the subject, is signally illustrated by the fact, that, whereas Pitcairn had allotted to the stomach fibres such an enormous power, Borelli thought that 1350 pounds was more correct. Hales believed that 20 pounds would come nearer the truth, and Astruc valued its compressive force at 5 ounces.

It was many years, in fact the greater part of a century, before further contributions were made to the knowledge of the subject of digestion. It is true that at the close of the 17th Century and the beginning of the 18th Century, there flourished two men who achieved great eminence as chemists and who were assiduous in applying their chemical knowledge to physiology; but, so far as digestion is concerned, their influence was rather that of expositors than that of discoverers. I refer to George Ernest Stahl, born in 1660 at Anspach, and Hermann Boerhaave, born near Leyden in 1668.

Stahl, employing the term Animism, ascribed the force used in digestion, as well as in all the chemical changes taking place in the living body, to the "sensitive soul." His conception had not a little kinship to van Helmont's; indeed, his views may to a certain extent be regarded as a development of it. The sensitive soul of Stahl is that of van Helmont with two differences only. It works directly on chemical processes, without the intervention of *archæi*, and is not a mortal something associated with, and as it were the shell of, an immortal mind, but it is itself the immortal principle, spiritual and immaterial, coming from afar, and at the death of the body returning whence it came.

Speaking of the physiology of digestion, Stahl seems to admit fermentation as a property of non-living things and to regard putrefaction also as a sort of fermentation, possible in and belonging to non-living things. Apparently, he regards the ferments of saliva and pancreatic juice as non-living agencies, although he refuses to believe in a gastric ferment.

Boerhaave (1668-1738), the teacher of Haller, was a man of wholly different mind and, although a learned scholar and a sound scientific thinker, he cannot be said to have made any striking contribution to our knowledge of digestion. Essentially eclectic in nature he combined in his conceptions of physiological processes many of the doctrines of earlier systems.

He recognized that digestion was, in part at least, a solution of some of the constituents of the food by means of various juices. Saliva, the juice from the esophagus, the gastric fluid, which consists in part of a viscous secretion poured out by the glands of the stomach, and in part of a thin fluid secreted by the arteries, the bile, the pancreatic juice, and the intestinal juice, each of these contributed to the result. But he regarded the solution effected by means of these juices as of the nature of an ordinary solution, and not of a fermentation. He denied the acidity of the gastric juice. In common with his contemporaries, Boerhaave regarded the nerve supply to the stomach as out of all proportion to the movements or sensations of that organ and believed that a nervous fluid, having some share in the digestion of food, was poured into the cavity of the stomach from the endings of the nerves.

He joined with the mechanical school in believing that the more fluid and nutritious parts of various articles of food were expressed from them by trituration in the stomach. In particular he thought that bones were not digested, only crushed. He was more or less antagonistic to the doctrines of fermentation, and regarded the action of the juices as a mere solution, not as a proper fermentation. Nevertheless, he held that solution and trituration are, in digestion, aided by something else. He thinks that the stomach contents, being exposed to considerable heat, undergo "an incipient fermentation by means of which the chyle is impressed with the primary principle of vitality."

These doctrines of Boerhaave became the dominant ones for many years; indeed they were taught by his illustrious pupil, Haller, nearly fifty years later.

Albert von Haller was born at Bern in 1708 and in 1725 went to Leyden to work under the renowned Boerhaave, where he undoubtedly laid the foundation of all his future work. Haller was a universal and indefatigable savant, of ingenious natural endowments, a marvelous, almost unique, capacity for work, absolutely conscientious, a man of inextinguishable love for science and art, and one of the greatest medical thinkers of all times, as well as a notable poet, botanist and statesman.

[11] Regarding the presence of this corrosive juice in the stomach and its influence upon digestion, we find that the followers of Borelli went beyond their master and were prepared to deny chemical action in all cases and to maintain that digestion was in reality a mere trituration of the food by the muscular mill of the stomach into the creamy mass known as chyle.

In 1757 he began to publish his "Elementa Physiologiæ," the eighth and last volume leaving the press in 1765. This great work may be taken as a trustworthy account of the knowledge of the time with regard to the questions therein stated.

In his exposition of digestion he considered the saliva to be neither acid nor alkaline and regarded its use as being that of softening the food and helping deglutition. He recognized the importance of the tunica villosa of the stomach, but says that the glands therein contained furnished the mucus of the stomach only, the true gastric juice, the succus gastricus, being secreted by the arteries. He discarded the idea of Boerhaave that a nervous fluid, oozing from the endings of the nerves, intervened in gastric digestion. He believed that pure gastric juice was neither acid nor alkaline, and while speaking of it as a macerating liquor which softens and dissolves the food, he refused to regard it as a ferment. He held that it was not a corrosive liquid, like many acids, and, though at times it might be acid, the acidity was a token of the degeneration of the digested food, not of digestion itself.

He regarded trituration as a useful aid, especially where hard grains form a part of food, as in that of birds, but only an aid. "They have done well who have brought back to its proper mediocrity the power of trituration so immensely exaggerated."

He looked upon bile not as a mere excrement, as some had done before him, but as a secretion from the liver substance. It was a fluid viscid and bitter, but not acid, and indeed not alkaline, a fluid which had the power of dissolving fat. He added that the bile must have some other function than that just described; "for animals deprived of their gall-bladder very rapidly perish, the exact cause of their death not being clear."

In considering the pancreas he says, "A part at least of the usefulness of pancreatic juice will be to dilute and soften the cystic juice, so that this mixes better with the food." He adds, "There may be other functions of the liquid not as yet well known to us"—a sentence perhaps prophetic of the work of Bernard a hundred years later.

In this brief review of the opinions and theories of the eminent men of science living before the middle of the 18th Century regarding the subject of digestion, we find that to van Helmont the stomach with its acid character was the important organ of digestion; that others following him insisted that other juices were of more importance but that most of them, though they admitted a certain potency to the gastric juice, either doubted or denied its acidity. The veil of doubt was, however, soon to be lifted, and thus to reveal the true nature and function of the gastric juice.

The year 1752 is indeed a red-letter year in the history of our subject. In that year were published two treatises upon the "Digestion of Birds" by René Antoine Ferchault de Réaumur, which mark an epoch in the history of digestion by indicating the dividing line between modern ideas of physiological processes and all that had gone before. Réaumur was one of the most striking men of science of the 18th Century. Born at Rochelle, France, in 1683, he moved to Paris at the beginning of the 18th Century. He was a wealthy man and used the opportunities thus afforded him in carrying out many and varied scientific experiments. But it is only of his work on digestion of birds that I shall now speak. In these experiments he attempted to learn whether the digestion of food was due to trituration, putrefaction, or to solution, brought about in some way by means of the gastric juice secreted by the stomach. He devised a means of determining whether the comminution and solution of food is effected by the action of the gastric muscles. This he accomplished successfully by obliging animals to swallow metallic tubes opened at both ends, save that each end was secured with a grating made of threads or fine wire, and filled with their natural food, such as grains, etc., for granivorous fowls. He argued that if these grains, after remaining in the stomach, were broken down and decomposed, we must assign a dissolving liquor as the cause of the phenomenon, since the sides of the metallic tubes must have presented an insuperable obstacle to the action of the gastric muscles upon the contents; but that if they were returned in a sound and entire state, it must be acknowledged that in these animals digestion does not depend on a solvent, but on muscular action. His first memoir deals with digestion in granivorous birds—those possessing a gizzard or muscular stomach.

A few hours after they had swallowed the grains, Réaumur killed the animals and removed the tubes for examination. He found barley grains, etc., quite entire, whence he inferred, that in these animals, the food was not broken down by a solvent, but by the strong action of the muscular stomach. He further observed that if the tubes were quite thin, they were frequently broken, crushed or distorted in a most singular manner. These results need not surprise us if we but recall the observations of Redi and Borelli, that ducks, fowls, and pigeons pulverized hollow globules of glass in a very short time.[12]

"This hypothesis of Vallisnieri is evidently groundless," says Spallanzani, "for seeds remain unaltered whenever they are defended by tubes. As when pigeons, fowls and turkeys are forced to swallow several balls of glass at once, some in tubes and others naked, the latter are reduced to small fragments as usual, while the former remain entire. The gastric muscles are the chief cause of this effect."

It had been long known that fowls always have a supply of pebbles in the stomach. It was observed by Redi, Borelli and others, when members of the Academy of Cimento, which was established in 1657 under the patronage of Prince Leopold, that the ducks and fowls that had the greater number of stones in their stomachs more quickly reduced spheres of glass to powder. Redi thought that the stones performed the office of

[12] It may also be of historical interest to mention that Vallisnieri of Padua (1661-1730) stated in his anatomy of the ostrich, that the hardest substances, such as stones, wood, glass and even iron are reduced to pieces in the stomach of these enormous birds by a solvent. Moreover, he was inclined to think that glass was attacked and broken by a similar liquor, which he believed existed in the stomach of fowls, without the concurrence of muscular action.

teeth, while Réaumur believed that they were necessary to digestion.

The greatest part of Réaumur's first memoir deals with the great force of the gizzard of fowls in triturating the food; in the remainder he endeavors to prove that this viscus contains no menstruum of sufficient efficacy to produce solution. In support of this he mentions the following points based upon experiments: (1) Barley grains remained unaltered within the tubes; and (2) ducks were given small particles of meat in tubes and on removal from five to twenty-four hours later, some pieces had retained their red color (some, however, had lost it) and there was also no appreciable diminution in amount. From this he inferred that no menstruum had acted on the meat, since it was not comminuted or much dissolved, and he even concluded that the gizzard contains no solvent capable of decomposing and digesting the aliment.

In his second memoir he inquired into the nature of the function of digestion in carnivorous birds, whose stomachs are membranous in type. He chose a kite as the subject of his experiments, taking advantage of its well known habit of vomiting indigestible things which it had swallowed. He used tin tubes filled with different substances, especially meat, which were thrown up, after a certain time; and that the meat was more or less digested, according to the time it was in the stomach, was the general and invariable result observed. Hence, he justly inferred, that here digestion is produced by the gastric fluid, without the concurrence of any triturating power. From other additional experiments he also concluded that digestion in other birds with membranous stomachs is produced in a similar manner.

On several occasions he had observed that when his tubes containing flesh and grain were rejected, they were filled more or less completely with a yellowish, somewhat opalescent fluid, which to the taste was salty and bitter. Obviously it was this fluid which had dissolved the food and he asks himself these questions: "What is this liquid which acts on flesh, but has not the same power on starch? To which of the solvents which chemistry offers us can this liquid be compared?" To answer these questions he filled his tubes with small pieces of sponge, from which, when rejected, he squeezed out the fluid which they had imbibed. In this way he obtained a small amount of an opalescent fluid, salty to the taste, rather than sour. By this means he was the first to obtain gastric juice in an approximately pure condition.

With the fluid he attempted a few experiments in artificial digestion by allowing it to act upon particles of meat at 32° R. for twenty-four hours, using meat placed in water as a control. He found that, while the meat in the control putrefied, the portions placed in the gastric juice, though not very much dissolved, were hardly at all putrefied. Hence, he concluded that digestion was not putrefaction, but something quite opposed to that process. He lamented, however, that, from the death of his kite and his neglecting to substitute other animals in its stead, he could not adduce facts sufficiently numerous to illustrate the subject more fully. He promised to supply the deficiency on some future occasion, but his death a few years afterwards (1757) prevented him from fulfilling his promise.

Of course, these experiments of Réaumur still left a great deal to be investigated, but their value lies chiefly in the following: He employed an entirely new method in the investigation of gastric digestion. He further established the fact that the gastric liquor possessed a distinctly solvent power, dissolving various constituents of food, not by inducing or favoring putrefaction, but by a process which was quite antagonistic to it.

The next solid contribution to the subject of gastric digestion was made by Spallanzani,[12] some twenty-five years after the epoch-making investigations of Réaumur.

This scientist contributed much to our knowledge of physiology and natural history, but it is of his work upon the physiology of digestion that I wish to speak. Practically all his experiments and discussions are contained in his "Dissertations Relative to the Natural History of Animals and Vegetables," the original Italian publication first appearing in 1782.

Spallanzani's methods of experimentation were those of Réaumur, but he greatly enlarged upon them. He employed thin metallic and wooden tubes opened at one or both ends and covered with wire grating. He perforated the sides also of the tubes to allow freer access of the gastric liquor. He also used hollow brass globules divided into hemispheres, which were pierced like a sieve, and which he could open and shut at pleasure. In some cases he employed small linen sacs, using one to four thicknesses of cloth whereby he thought to partially prevent, or to increase, the action of the gastric liquor according to the thickness of the cloth. In other cases he introduced into the stomach or esophagus, meat, etc., tied to a wire or string, fastening the free end around the animal's neck. This method permitted him to withdraw the food at any time during the process of digestion, and examine it. He even introduced long cylinders containing meat, bread, etc., allowing one end to rest within the stomach and the other in the lower esophagus, and in this way was able to observe digestion in the stomach and esophagus at the same time. He employed, as did Réaumur, small sponges to obtain the gastric liquor, with which he made numerous experiments in artificial digestion. On himself he experimented by swallowing these small, thin linen bags, containing various kinds of food, examining the contents after they had been voided *per anum*. He even dared to swallow wooden tubes. Finally, he obtained gastric liquor by making himself vomit on an empty stomach before breakfast. He employed a great variety of foods in these experiments, such as grains of all kinds—wheat, corn, maize, rye, etc.; flesh of every description; also animals, including fishes, frogs and earthworms; and finally, ligaments, cartilage, hard and soft bones, teeth and coral.

[12] Born in 1729, at Scandiano, in Southern Italy. He became professor of Logic, Mathematics and Greek at Reggio at the age of 25, but in 1760 was transferred to Modena, where he filled the chair of Natural History. In 1768, he became professor of Natural History at the famous University of Padua, where he labored until his death in 1799.

His experiments were very numerous and included practically all species of animals. He first investigated digestion in animals that possessed muscular stomachs or gizzards; these included common fowls, turkeys, ducks, geese, doves, and pigeons. His second dissertation deals with animals that possess the so-called intermediate stomach, namely, crows and herons. The experiments outlined in the third, fourth and fifth dissertations were performed upon animals with membranous stomachs, these including frogs, newts, earth and water snakes, vipers, fishes, sheep, oxen and horses; also, the little owl, screech owl, falcon, eagle, cat, dog, and finally man. His last dissertation deals with the question, whether food ferments in the stomach, and also with the question of the acidity of the gastric juice.

Spallanzani by innumerable experiments carried on in the various ways which I have mentioned, confirmed and greatly extended Réaumur's results. His conclusions were many, and I shall state them as briefly as possible:

SPALLANZANI'S CONCLUSIONS.

In Animals with Muscular Stomach or Gizzards.

1. Trituration by means of the muscular walls of the stomach is the chief factor in the digestion of grains and the like, though the gastric liquor undoubtedly assists it.

2. Trituration and the action of gastric juice mutually assist each other in the digestion of flesh; the former breaking down the aliment, acts as a predisposing cause; the latter, when it is thus prepared, penetrates into it, destroys the texture, dissolves the particles, and disposes them to change their nature and to become animalized.

3. The stones that are always found in the gizzards of these animals are not at all necessary for the trituration of firm food and even harder substances, contrary to the opinion of many anatomists and physiologists, ancient as well as modern. When, however, they are put in motion by the gastric muscles, they are capable of producing some effect upon the contents of the stomach.

4. The digestion of flesh and bread may take place solely by the action of the gastric juice without any assistance from the triturating action of the gastric muscles.

5. Gastric liquor retains outside the stomach the power of dissolving animal and vegetable substances in a degree far superior to water. (He advises the use of heat and fresh gastric juice.)

In Animals with Intermediate Stomachs.

1. Gastric liquor of crows is a solvent of flesh without the aid of trituration.

2. The digestion of food is proportional to the quantity of gastric juice acting upon it.

3. Bones are undigested by the gastric juice of crows, except soft ones, like cartilage, which are digested very slowly.

4. Flesh is very slowly digested by esophageal liquor.

5. Crows' gastric liquor is of a transparent yellow color, which deposits very little sediment on standing, possesses a bitter and salty taste, has very little volatility and is non-inflammable.

6. Gastric juice, outside the body, digests flesh without the production of putridity. Digestion is enhanced by heat and is more rapid when gastric liquor is allowed to flow slowly over the flesh and constantly renewed. Digestion is retarded by cold.

7. Gastric juice is secreted by small arteries, which open into the stomach. (He was not sure of the presence of any gastric glands which might serve such a purpose.)

8. Some power of trituration is present in the stomach of the heron, but digestion here is not the effect of the trituration, but of the solvent power of the gastric juice. It has even the power of digesting bones.

9. The bitter taste of the gastric liquor derives its origin from the bile which regurgitates through the pylorus into the stomach cavity.

In Animals with Membranous Stomachs.

1. In frogs, gastric juice was found to have slow digestive powers.

2. Water-newts digest fish-worms in twenty-four to forty-eight hours without the intervention of trituration.

3. Digestion of food in frogs, serpents, water snakes, vipers, eels, carps, barbels and pikes is performed by the gastric juice, though somewhat slowly. No trituration is present.

4. In sheep and oxen the process of rumination precedes the solvent action of the gastric liquor. No triturating power is present.

5. The gastric fluid of the little owl can digest bones as well as flesh. It does not become putrid even when exposed for months in hot weather. Esophageal liquor from this animal also digests flesh quite rapidly. (He obtained similar results with the tawny owl.)

6. The gastric juice of the falcon digested bone and tendon quite rapidly, as well as flesh, but did not have much effect upon teeth, enamel or horn. Trituration is not a factor.

7. In the eagle such substances as bread and cheese and flesh and even bone were quite readily acted upon by the gastric juice outside of the body. The gastric juice of this bird digested animal and vegetable substances. It produced an incipient solution of bone and almost a complete one of cartilage.

8. The gastric fluid of the dog and cat is the efficient cause of digestion in these animals, independently of any triturating power. In the dog it also acts upon bone, but not so speedily as upon flesh, because of its hardness.

9. There is a peristaltic motion of the stomach of dogs and cats and some other animals, which was demonstrated by opening the abdomen shortly after feeding. It was easily excited by irritating the stomach with a knife point, which produced contraction followed by an undulating wave across the stomach and by a dilatation of the contracted portion. This gradual movement of contraction and dilatation began at the upper end of the organ and extended to the lower and (he felt that) this motion was calculated, not to triturate the food, but to carry it slowly from the superior to the inferior orifice of the stomach, and thence to expel it into the duodenum.

10. In the experiments upon himself he found that flesh and bread were rapidly digested by his gastric juice independent of trituration, and that it could dissolve muscle fibres, membrane, and even tendon, cartilage and soft bone, though the time consumed in digesting the latter substances was somewhat longer than in the case of the former. "Before quitting the subject," he says, "let me observe that though I have mentioned the gastric juice as the efficient cause of digestion in the experiments upon myself, yet I mean not to exclude those of the intestine from their share. We know that the small intestine completes the process of chylification, which is but begun in the stomach. I must allow, therefore, that the digestion of animal and vegetable substances in the bags and tubes is perfected in the intestine. But this is not in the least repugnant to the results of those experiments that show the human stomach to be destitute of any triturating force, and digestion to be the effect of the gastric juice alone, though the fluid which is secreted by the side of the small intestine may complete the process."

11. The gastric fluid obtained from his own stomach was a little salty to the taste but not especially bitter, and possessed no prop-

erty of inflammability. Gastric juice left in a phial one month did not become putrid. Beef was quite readily dissolved when kept at a definite heat and did not putrefy, but the control in water became excessively putrid in a short time.

12. The gastric juice is probably provided with an antiseptic principle. When acting upon flesh, etc., outside (or inside) of the body, it rarely, if ever, putrefies. In fact, it impedes putrefaction and in some cases may even restore putrefied substances. None of the three species of fermentation (sweet, acetous or putrid) takes place in digestion.

13. There is present in the stomach of man and some animals an acid principle, but it is not constant and depends on the quality of food. This temporary acidity is not produced by the gastric fluid, but by the food. (He sent a specimen of the crow's gastric juice to Scopoli, the eminent chemist, for analysis—apparently the first detailed analysis on record. The results of this and his own examination led him to the conclusion that the gastric fluid was neither acid nor alkaline, but neutral. He thinks, however, that there may be a latent acid in this fluid, though it cannot be detected by any of the ordinary means. His reason for this was the observation that it readily curdles milk—a fact held by Macquer and others to be a sign either of a manifest or occult acidity.)

We thus owe to Spallanzani, after Réaumur, the definite experimental proof of the solvent power of the gastric juice upon various constituents of food, but he was unable to go much beyond this, because he failed to recognize its acid character. He, however, conclusively disproved the older theories of digestion, especially that of trituration, putrefaction, fermentation and maceration.

I have dwelt at some length upon the investigations of these two men because it seemed to me that they were pregnant with many suggestions for future scientific lovers of truth. Their work is in reality the germ from which many of our more modern ideas concerning the physiology of digestion have sprung. During the next fifty years numerous monographs appeared dealing with various phases of digestion, and I deeply regret that I could not have brought the subject up to a more recent date. But, before closing, it might be of interest to mention briefly some of the more important additions which were made during the half century following the work of Spallanzani.

In his physiological inaugural dissertation, entitled "De Alimentorum Concoctione," Stevens of Edinburgh, in 1777, adopting the methods of Réaumur, substantiated the work of the French and Italian inquirers. In 1772, appeared a paper by John Hunter, published in the Philosophical Transactions, "On the Digestion of the Stomach after Death." This was followed, in 1786, by his "Observations on Digestion," both of which papers contain many interesting facts and observations relative to our subject. It is very evident, from a perusal of these articles, that Hunter entertained views on digestion which are very similar to those of Spallanzani, though modified by the vitalistic Stahlian conceptions, in which the latter did not share. Hunter at first was inclined to attach considerable importance to the acidity of the gastric juice. In 1772, he writes, "In all the animals, whether carnivorous or not, upon which I made experiments to discover whether or not there was an acid in the stomach (and I tried this in a great variety), I constantly found that there was an acid, though not a strong one, in the juice contained in that viscus in a natural state." But in his later communication he says, "It is only found occasionally." And, indeed, the 18th Century passed wholly away before the "acid ferment" on which van Helmont had, in the early years of the 17th Century, laid such great stress was rightly appreciated; for the observations of Carminati, who in 1785 found the clue to the problem of the acidity of gastric juice, by showing that in carnivora at least the juice, though neutral when the animal is starving, is undoubtedly strongly acid after it has been fed, fell on barren ground.

We have seen that numerous theories as to the nature of the digestive process, before the time of Spallanzani, were held by physiologists. That of *coction* was entertained by Hippocrates, Galen and others; *putrefaction* by Praxagoras of Cos, and apparently, even by Chelseden (1688-1752); *trituration* by Erasistratus, Redi, Borelli, and others; while the theory of *fermentation* had many partisans, amongst whom may be mentioned, van Helmont, Sylvius, Willis, Grew and Lower. Even Haller adhered to the theory of maceration, supposing that the food is merely diluted and softened by the stomach fluids. Finally, we have the theory of *chemical solution*, proposed by Spallanzani, a theory which met with more favor from physiologists than any of the others.

To such a turbulent state of knowledge, the well known pithy and laconic observation of William Hunter was certainly not out of place, "Some physiologists will have it, that the stomach is a mill, others that it is a fermenting vat; others again, that it is a stew-pan; but in my view of the matter, it is neither a mill, a fermenting vat, nor a stew-pan, but a stomach, gentlemen, a stomach."

In 1803, Young, of Baltimore, experimenting upon frogs, snakes, and other animals, demonstrated that the solvent power of the gastric juice is due to its acid content, which turned litmus paper red. He further showed that it had its origin in gastric secretion, and that it did not originate from any kind of fermentative process, vinous or otherwise. He also deduced the important fact that the flow of gastric juice and saliva are associated and synchronous, a point which has but recently been demonstrated by Pawlow and his collaborators. He made the error, however, that it was phosphoric and not hydrochloric acid that was present. It was not until twenty years later (1824) that Prout (1785-1850) of England proved that hydrochloric acid was the free acid in the gastric juice.

Prout was speedily followed and his statement affirmed by Tiedemann (1781-1861) and Gmelin (1788-1853) in their notable monograph "Die Verdauung nach Versuchen," which appeared in 1826-27.

Six years later, in 1833, there was issued from the press a volume entitled, "Experiments and Observations on the Gastric Juice and the Physiology of Digestion," which contains the classical and far-reaching investigations of William Beaumont (1785-1853) a surgeon of the United States Army, upon the young Canadian voyageur, Alexis St. Martin, who was accidentally shot in the stomach (1822), the wound healing after a year or more with the production of a gastric fistula,

the aperture being about two and one-half inches in circumference. Beaumont at once seized the opportunity which presented itself in this remarkable case, and at different periods during the following nine or ten years he performed numerous experiments, 238 in all, with this Canadian half-breed as the subject of his investigations.

Several cases of artificial gastric fistula had been reported before the time of Beaumont's work, but the case in point stands out pre-eminent above all others on account of the accuracy and care with which the experiments were performed.

As we have seen, much uncertainty existed in the minds of men as to the exact nature of the phenomena occurring during digestion in the stomach, the precise mode of action of the juice, the nature of the juice itself and its action outside the body. On all these points Beaumont's investigations brought clearness and light where there had been previously the greatest obscurity. Perhaps, the most important observation was his study of the digestibility of different articles of diet in the stomach, which remains to-day one of the most important contributions ever made to practical dietetics. His observations are probably the most important ones until the time of Pawlow and his school who, chiefly by perfection in technique of experimentation, were able to carry the work further. Beaumont was truly the leader and pioneer of experimental physiology in our own country.

In looking back over the centuries and tracing the historical development of the various systems and theories which were formulated from time to time by the greatest physicians, scientists and philosophers of their day, we are unable at the present time to appreciate at their true value the circumstances under which they were formulated, and the advantages or disadvantages attendant on their conception. But it must remain an element of surprise and disappointment that the views current up to the close of the 18th Century should show so slight an advance over those formulated, with less particular knowledge, two thousand years before.

No less surprising is the wonderful advance which has been made since the beginning of the 19th Century in the elucidation of physiological problems. Coincident with the onward progress of science our knowledge of the chemical and physiological processes which serve to support life has remarkably increased. Thanks to the patient investigation of the infinitely little, and to the gathering together of the results, theories of vital processes can now be based upon multitudes of observed facts, giving both positive and negative evidence.

By following the teaching of Hippocrates in 400 B. C., teaching which was until lately disregarded, or at least spasmodically and superficially followed, we have penetrated many of the mysteries connected with bodily processes, though much still remains to be done.

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PROCEEDINGS OF SOCIETIES.

THE JOHNS HOPKINS HOSPITAL MEDICAL SOCIETY.

JANUARY 3, 1916.

1. **Seminal-Vesiculectomy in Arthritis.** Dr. H. H. Young.

DISCUSSION.

Dr. Quinby: I can only call your attention to one or two further points with regard to the seminal vesicles. I have felt that the development of the surgery of these organs is a subject of which American surgeons should be very proud, because, although they were described, as were so many other structures of the human body, by Fallopius in the sixteenth century, and of course were known by all subsequent anatomists and surgeons who were not afraid to attempt surgery on them, still it remained for American surgeons, and above all for the present generation of American surgeons, to demonstrate a successful surgical approach to these organs. As one looks over the literature of the subject to-day one finds instead of a long list of German, French, Italian, Polish, and Russian names, that the contributors are almost entirely American. This is due to the fact that American ingenuity was applied at the time when the European surgeons had given up serious, radical

attempts on these organs. The work, as Dr. Young has mentioned to you, was started first in this country by Dr. Belfield of Chicago, and by Dr. Fuller of New York, but it was not until such deft operators as the president of this society directed our attention to the subject, that successful excision of the vesicles was made possible.

Some may ask if the seminal vesicle, when normal, is of any special value except as a reservoir; or whether it has some function which should be preserved if possible. For a good while the idea prevailed that the vesicle was simply a reservoir for portions of the spermatic fluid. More recent physiological observations, especially on animals, have shown that, though this is true, it has other intrinsic functions. In some species the secretion of the seminal vesicle has agglutinating properties. For instance, in the rodents, more especially in the guinea-pig, the secretion of the seminal vesicle causes the prostatic secretion to coagulate. By this method nature provides in two ways for successful impregnation. By coagulation the material is prevented from leaving the vagina after coitus, while at the same time the spermatozoa are squeezed outside the coagulum so that they can exert their normal activity unhampered. In various other ways also the secretion of the vesicle is important. For instance, it has been shown that reproduction is not impossible after extirpation of the vesicle, but that the fruitfulness of such an animal is decreased.

I quite agree with Dr. Young's conclusions that if one is operating on a vesicle which is so diseased as to necessitate exploration, it should be removed in the large majority of cases.

DR. HUNNER: It does not seem necessary to emphasize the importance of this subject—the rôle played by the genito-urinary organs in furnishing a focus for widespread infection. In the female we do not see many cases in which arthritis can be traced directly to the genitro-urinary organs. Of course, the genitalia have the deep glands of the cervix and the Fallopian tubes, which, becoming infected with gonococci, occasionally form foci for infections of the joints. In the urinary tract we do not have to deal with the deep glands characteristic of the male, and for that reason we see far fewer cases of general infection or arthritis derived from the urinary tract of the female.

I have been particularly interested for the past few years in infections which come to the genito-urinary tract from other foci, such as tonsils, teeth or sinuses. I hope in a short time to bring before the society a series of 50 cases of stricture of the urethra, in a good many of which, I am satisfied, the infection that started the infiltration about the urethra came from some distant point, such as the tonsils, teeth or sinuses.

I have been interested in the male side of this question, more particularly because of the women who have come to me complaining of sterility. It seems strange that, even to-day, women go about from gynecologist to gynecologist being treated and curetted because they are sterile and anxious to become pregnant, while the logical and simplest method of finding out what the real trouble is in a good many cases is to have the male examined. In from 40 to 50 per cent of these cases, on examining the secretions of the male, we find the sterility in all probability is due to blocking or obstruction of the spermatic organs.

Certainly those interested in genito-urinary work in the male will feel a great debt of gratitude to Dr. Young for these methods which he has presented to us to-night.

DR. GUTHRIE: It is, of course, a matter for congratulation that another possible focus of infection has been discovered. We have felt for a long time that there were foci that were not being approached, and particularly ones which were apparently cryptic and which do not present symptoms which would lead to suspicion being cast upon them. One great difficulty which is encountered by all those who try to arrive at a diagnosis in infectious arthritis is the multiplicity of possible foci and sometimes of actual foci which may exist. The question then arises as to which one is the seat of the trouble. In a recent case on the wards, the patient was discovered to have abscesses about the roots of the teeth. Despite the protests of the patient, these were removed. The next thing was an examination of the sinuses and the remains of the tonsils. One diseased tonsil was discovered and also eliminated. Following that an examination of the digestive tract revealed a difficulty about the appendix. This was investigated and, the suspicion that there had been trouble in this area having been confirmed, the appendix was removed. Following each one of these procedures, the patient improved considerably, but I have a letter to-day saying that her symptoms have returned. Apparently the search for the guilty focus must be resumed.

2. Tuberculosis of the Tonsils. DR. S. J. CROWE.

JANUARY 17, 1916.

1. Methods and Results of Direct Transfusion. DR. R. D. MCCLURE and DR. GEORGE DUNN.

To appear later in the BULLETIN.

2. The Clinical Significance of the Wassermann Reaction. DR. ARTHUR F. COCA.

DISCUSSION.

DR. MILLER: I am extremely interested in the message brought this evening. It brings up the question in one's mind as to whether the Wassermann reaction is worth anything, or any treatment is worth anything in lues. From the scheme drawn on the board, I am not prepared to answer, off hand, which of the conclusions one can justly arrive at.

There are a few points I would like to take up briefly. First, Dr. Coca made the statement that the reagents employed in the Wassermann reaction are very unstable and vary from day to day. I think that is open to some argument. Patients' serum is an unknown variant. The amboceptor which has been suitably prepared has, I believe, usually been regarded as quite a stable thing. That is, given an amboceptor of a given titre, it does not vary much from time to time provided it is kept under suitable conditions. The suspension of sheep's red blood cells, freshly prepared, is a presumably stable reagent. Each new lot of complement is stable during the period in which it is used, and its power is determined by suitable preliminary titrations. Any given antigen suitably titrated from time to time is constant, in that you know what it will do, at least relatively. If, however, one takes the various short cuts designed to be useful and time saving, then a number of these preliminary titrations are omitted and one is dealing with a number of variable reagents, and presumably some of them at times are absolutely inert. So I should think a possible criticism of the statement of their variability might be taken into consideration from that standpoint. Out of the first 1200 cases admitted to the Phipps Psychiatric Clinic, all cases were routinely tested against three different antigens—the cholesterinized extract of human heart (.04 cholesterin), a similar extract of the same heart not cholesterinized, and the acetone insoluble lipoid fraction prepared according to the Noguchi method. These were all tested for their binding powers, and we knew what each antigen would do in terms of the other two. Out of the first 1200 cases, the results with these three different antigens, in all cases of known, unknown or suspected lues, were identical, except in seven cases. In those seven, the cholesterin extract gave a positive fixation, while the other two were negative. This was in our minds suspicious enough to warrant the repetition of the Wassermann on those individuals' blood taken a week later, and also a control done by someone else who had known nothing about the condition. In all seven instances, the result came back the second

time exactly the same and was confirmed from one or two other sources. In my experience even two antigens are not enough to be invariably useful, for there are differences between antigens that apparently bind equally well with a known positive serum, which we do not yet know.

As regards the one particular point that interested me most—the finding of the uselessness of the Wassermann reaction in non-luetic and in unsuspected cases—it seems to me that there may be fallacies (and I am not by any means certain that the Wassermann reaction is free from fallacies), yet all the weight of evidence is against the statement. There have been too many instances where a definite luetic process has been confirmed by the subsequent course of the case, either at autopsy or by following suitable therapy. I do not believe that the Wassermann reaction is a bio-chemical one. I believe it will be shown to be a purely chemical process, essentially a colloidal chemistry affair. There is evidence for this that has apparently been buried away in the literature. It has been definitely suggested by Paul Schmidt that the sera of luetics differs colloidally very markedly from the sera of normal individuals. It seems to me that discrepancies in results will ultimately be explained on the basis of colloidal chemistry. I simply throw out the suggestion as being a possible source of hope in this apparently hopeless tangle.

Dr. Keidel: I would like to say that I agree with Dr. Miller's remarks on the various reagents that we use; and to add that with our titration of the complement I think we can always eliminate that as a source of error, provided we maintain a high standard for it. We have always felt that we must be continuously making new antigen preparations. While we do not adopt a unit of titre, we, nevertheless, use a comparative method of investigating them. We run more than one antigen in the series and try always to have a new antigen running with the others. If the new one does not come up to the standard of the antigens we have been using, we discard it. In this way we keep up an antigen standard which it seems to me must always be, if anything, slightly on the increase so far as efficiency is concerned. These antigens, of course, are always controlled for objectionable qualities such as would give a false positive. There are differences which have not been mentioned so far, which might account for some of the lack of uniformity in results, for we have observed that the sera of syphilitic patients reach a stage, particularly in treated cases, where there is a great variation from day to day in the amount of fixing body in the sera, that is to say, there is a zone in which the patient may vary, so that one day his sera may contain more fixing bodies, sufficient to give a positive Wassermann, and another day these may fall, so the Wassermann result would be a doubtful reaction. Another time they may fall so low that the reaction is completely negative. We have seen this repeatedly, in fact in almost all our treated cases this variation occurred. This would not, of course, be brought out unless a great many tests were made. We make frequent Wassermann tests. Our patients on treatment are in many cases tested every week, and always once a month.

With regard to the indictment of the Wassermann reaction, I do not think we are prepared to agree here with Dr. Coca's list of answers. We would certainly treat a typical hard chancre, with a history and with no secondaries, although the spirochætes are absent. In the first place such a lesion might easily not have spirochætes, because we know they tend to decrease in number as the lesion tends to heal, so that, even though the chancre may be typical, it may be perhaps at a late period, and we might fail in such a case to get spirochætes. In the second place, we know from experience here, and I am sure they do in other places, that the effect of treatment, particularly that of salvarsan, is so striking that we can make a diagnosis of a chancre practically by that alone, and with that as an aid we find we are justified in reading a positive Wassermann as an indication for immediate treatment in those cases. In such a case with a negative Wassermann, while the chancre may appear to be a typical one, we have still to remember that it may be a chancre redux or a tertiary lesion. Some cases of chancre I am sure are overlooked which at least should be recognized as chancre redux. In those cases there would be no spirochætes, and, the lesion being tertiary, there might be a negative Wassermann. I would be in favor of treating those cases at least as a diagnostic means.

In the second group of cases, we probably agree. In cases of typical chancre and secondaries, we would undoubtedly treat under A. Under B we would treat tentatively at least, with the idea that if we got no result from treatment, we would suspect some other condition.

In the third instance, we would not treat, because we would insist upon having a Wassermann test first. In the third group, we make our diagnosis clinically, regardless of the Wassermann reaction, if we feel sure enough to diagnose a lesion as a tertiary syphilide. There is a chance, of course, that the Wassermann may be negative in about one-third of the cases. If we made a diagnosis clinically, we would undoubtedly treat the case whether the Wassermann was positive or not. In obscure cases, I can only say this, that several years ago I analyzed with Dr. Frontz some 4000 cases in which we had made Wassermann reactions for diagnosis. We divided our cases into several groups according to the history and manifestations. Each group was subdivided into treated and untreated cases. While I am sorry to say I cannot give the figures exactly, I can state, however, that as the presumptive evidence of syphilis increased from group to group, so did the presence of the positive Wassermann. In the groups of treated cases there was always a lower percentage of positive Wassermanns than in those untreated. This analysis showed us that, when using the Wassermann reaction as an aid to diagnosis in a large series of cases, the percentage of positive Wassermanns increased as the evidence in favor of syphilis increased.

I quite agree with Dr. Coca that it is an extremely difficult matter to pick out non-syphilitic cases and test them and get 100 per cent negative. There are bound to be so-called clinically latent cases which would fall in that group and give a positive Wassermann. In the treated cases, there is difficulty, because we use the Wassermann as an indication for treatment as long as it is positive. If the Wassermann reaction becomes negative, we have lost a means of following the effect of the treatment. Our rule here, as a general thing, although we do not regard the degree of positiveness of the reaction as an indication of the severity of the disease, is to give a patient treatment and follow his Wassermann at frequent intervals. We know the time necessary to produce a negative Wassermann and use that as a basis on which to figure the amount of treatment that patient should have subsequently. The Wassermann undoubtedly then is of great assistance in treating those cases.

Dr. Miller: In this series of 112 cases in which the same two antigens were used by all five observers, it would be interesting to know if all five observers used a uniform technique. I think that makes a very material difference. It can readily be demonstrated that, given the same two antigens, two people in the same room at the same time, by different methods of mixing the antigens with salt, may get diametrically opposite results. Therefore, the series to have been of any value must have been comparatively the same all the way through, or else it cannot hold.

Dr. Coca: There is only one question that I have to answer—the question of Dr. Miller with regard to the technique used by the different men. You can anticipate what the answer will be—that it was humanly impossible for each one of these men to be under constant supervision in order to see that they did not put one thing in before the other, or the other before the one. It is, however, significant that Dr. Miller admits that two men standing side by side, using the same reagents, may get opposite results. His statement agrees with practically everything I have said.

THE JOHNS HOPKINS HOSPITAL HISTORICAL CLUB.

JANUARY 10, 1916.

1. **Jonathan Letterman and His Work in Organizing the Medical Department of the Army of the Potomac.** DR. JOSEPH T. SMITH.

To appear later in the BULLETIN.

2. **William Hunter, Anatomist, Physician, Obstetrician.** DR. C. W. G. ROHRER.

To appear later in the BULLETIN.

THE LAENNEC.

JANUARY 24, 1916.

Memorial Meeting to Dr. E. L. Trudeau.

The proceedings of this meeting appeared in full in the April number of the BULLETIN.

NOTES ON NEW BOOKS.

International Clinics. A Quarterly of Illustrated Clinical Lectures and Especially Prepared Original Articles on Treatment of Medicine, Surgery, Neurology, Pædiatrics, Obstetrics, Gynecology, Orthopædics, Pathology, Dermatology, Ophthalmology, Otology, Rhinology, Laryngology, Hygiene and Other Topics of Interest to Students and Practitioners, 1915. Vol. III. Twenty-fifth Series. (*Philadelphia: J. B. Lippincott Co.*)

It is not clear why the title "Clinics" should be applied to it, in view of the fact that fully one-third of the present volume is not in any sense clinical or even remotely connected with bedside practice. The papers entitled "One Hundred Thousand Men Minus," "The Ideal Physician as the Citizen-Builder," "The Advantage of a Library to a Medical Society," "Sanitation Among the Indians," "Defects in Our Public Insane Hospitals," "Mediæval Medicine and Medical Reform," "The Case Against Neo-Lamarckism" and "Therapeutic Technic" are interesting and profitable, but give one the impression of being essays originally prepared for another purpose, which have been "commandeered" by the enterprising editor. The sections dealing with Diagnosis and Treatment, Pediatrics, and Surgery, contain many admirable papers, of rather unequal length, but all worthy of attention.

Diseases of the Skin and the Eruptive Fevers. By JAY FRANK SCHAMBERG, A. B., M. D. Price $3.00. (*Philadelphia: W. B. Saunders Co., 1915.*)

There is always a place for a text-book which fulfills certain requirements. There are, of course, numerous excellent and satisfactory text-books on dermatology in English, by American authors, and it would seem that the addition of another would be entirely superfluous. It is well known that the complete text-book is of greatest use to the dermatologist himself, and that for the practising physician it is at times too comprehensive and encyclopedic in character. The kind of book which presents the subject briefly, clearly, and practically, both for the busy doctor and especially for the eager medical student is always welcome. The medical student has not the time, the energy, nor even the enthusiasm, to read a complete and comprehensive contribution on a dermatologic subject. For him especially, a short, readily comprehended, and even somewhat dogmatic, presentation is most acceptable and therefore most impressive. It is for this reason that a book like Schamberg's finds a most welcome place.

The entire subject matter of dermatology is covered and, in addition, there are sections on opsonotherapy, actinotherapy, radiotherapy, serologic procedures, and the acute eruptive fevers, including about a dozen acute infectious diseases accompanied at times by eruptions.

It is realized that a book of this kind must sacrifice much to brevity; yet it is to be regretted that the author has not written more fully on symptomatology in general, and on the rationale of treatment. A somewhat fuller discussion of the pathology of some of the commoner diseases would be advantageous from the standpoint of a more appreciative understanding on the part of the reader. For example the pathology of acne vulgaris is described in four lines. The discussion of X-ray therapy, which the author acknowledges has become such an important part of dermatologic therapeutics, is excellent, though not complete, since there is no guide to dosage, which after all is the principal point to be considered.

The text is well written; the illustrations are for the most part excellent; but, here again, it is to be regretted that more could not be used. The type is excellent, and the volume handy and attractive.

Especially noteworthy are the author's opinions, well and frankly expressed, on etiology and on therapeutics in particular—the things which give individuality to a text-book. He gives many prescriptions used in his own practice, written also in the metric system, and (fortunately for the student who is somewhat backward in prescription writing) written in full. He has presented a very sane conception of the treatment of eczema in general. The presentation of syphilis is excellent, even if not entirely comprehensive. Perhaps the most valuable contribution is the section on the acute exanthemata, on which the author is eminently qualified to write. The section devoted to eruptions associated with internal diseases forms a very desirable portion of the book and gives a very satisfactory conception of this very important part in the symptomatology of such diseases.

This book, therefore, should find a place in a field which is already replete with splendid contributions from American dermatologists.

I. R. P.

Progressive Medicine. A Quarterly Digest of Advances, Discoveries and Improvements in the Medical and Surgical Sciences. Vol. III, September, 1915: Diseases of the Thorax, Heart, Lungs, Blood Vessels, Skin, Nervous System, Obstetrics. Vol. IV, December, 1915: Diseases of Digestive Tract, Genito-Urinary Diseases, Surgery of Extremities, Diseases of Kidneys, Therapeutics. (*Philadelphia and New York: Lea & Febiger.*)

These volumes maintain the high character of the previous issues and contain interesting and valuable discussions on questions of the day, among which may be mentioned surgical shock, anæsthesia, infections, fractures, gastric and duodenal ulcer, and diseases of the kidneys. The various papers cannot be reviewed *in extenso* because of the great variety of topics which they cover, but are worthy of careful attention on the part of physicians and of students of medicine.

Applied Immunology. By B. A. THOMAS, A. M., M. D., and R. H. IVY, M. D., D. D. S. Price $4.00. (*Philadelphia: J. B. Lippincott Company, 1915.*)

This is a publication of 350 pages devoted to practical immunology, that is, to the methods employed in the preparation and administration of antitoxins, antibacterial sera, and vaccines. A mass of detailed information is presented in a systematic way and in general the author's aim of furnishing the medical profession with an exact knowledge of immunology and its conservative conclusions may be said to be fulfilled. The unfavorable results so often following the injection of vaccines are clearly brought out and the book will undoubtedly have a strong influence in combating the indiscriminate use of commercial preparations by practition-

ers of limited experience. We wonder if it is wise, however, to make such positive assertions as that on page 295, "Were the practice (typhoid vaccination) universal, typhoid fever would soon cease to exist." Certainly not, until methods have been established whereby individuals vaccinated against typhoid fever are more surely protected than at present seems to be the case. Nor does it seem proper to advocate the Coley treatment of sarcoma by the injection of "the streptococcus of erysipelas and bacillus prodigiosus," as is apparently done on page 303. A more extended experience of the medical profession in the field of practical immunology may clear up many doubtful points, and it may be hoped that in a future edition the authors will be able to tell us just what vaccines are of value and how far physicians are justified in administering them. W. W. F.

Alveolodental Pyorrhea. By CHAS. E. BASS, M. D., and FOSTER M. JOHNS, M. D. Illustrated. Cloth, $2.50 net. (*Philadelphia: W. B. Saunders Co., 1915.*)

This book has evidently been written by enthusiasts whose treatment of this disease, and clinical data, have been limited. The deductions drawn are not borne out by Koch's law; in fact, they are contradictory to it.

Endamœba buccalis is not recognized by investigators of acknowledged ability as an established etiological factor, its pathogenicity being seriously questioned. The clinical observations advanced in support of the treatment suggested are not sufficiently well founded, and it would seem that no justification exists for bringing this method into general use.

The practical value of this book to either the physician or dentist is questionable. L. D. C.

Trachoma—Its Prevalence, Its Effects Upon Vision and the Methods of Control and Eradication. By GORDON L. BERRY, Field Secretary, National Committee for the Prevention of Blindness. Price, $40.00 per thousand. (*New York: National Committee for the Prevention of Blindness, 1915.*)

A most interesting and instructive pamphlet, and, although written by a layman for the general public, contains a great deal that even the oculist can read with profit.

The illustrations, all from photographs, are unique and illuminating, and the statistics showing the virulence and wide distribution of the disease in this country will be a great surprise to almost everybody. H. H.

Lead Poisoning. By SIR THOMAS OLIVER, M. A., M. D., M. R. C. P. Cloth, $2.00. (*New York: Paul B. Hoeber, 1914.*)

This little volume on lead poisoning, by Sir Thomas Oliver, is the book form of the lectures on this subject delivered in the Royal Institute of Public Health, Russell Square, London. Ever since the discovery, by Dr. George Baker in 1767, that the "colic and palsy" common among the inhabitants of Devonshire, especially in those addicted to the use of hard cider, was simply lead poisoning, English physicians have been keenly alive to the danger that lead offers to the British workman.

These lectures give in a readable and pleasing manner the present state of knowledge on the subject. The subject is treated chiefly from the clinical standpoint and the book is singularly free from the dry statistical tables so often observed in works on industrial diseases. Of especial value is the closing portion which gives in detail the various regulations enforced in English factories for the prevention of saturnine intoxication. W. W. F.

Fever, Its Thermotaxis and Metabolism. By ISAAC OTT, A. M., M. D. Price $1.50 net. (*New York: Paul B. Hoeber, 1914.*)

This book consists of the collected lectures of Dr. Isaac Ott, delivered before the Sophomore Class of the Medico-Chirurgical College of Philadelphia. They form most interesting reading and enter in detail into the causes and metabolism of fever. The literature is most completely reviewed and referred to throughout the lectures. The various centers in the brain for the control of heat regulation are given and the experiments employed in their exploration presented in detail. Having finished up the discussion on thermotaxis or heat regulation in the first lecture, in the second, he takes up thermolysis or heat dissipation. Here again a description of numerous interesting experiments and descriptions of calorimeters is given. The third lecture contains a lengthy study of malarial fever in relation to the metabolism of fever and an account of certain investigations of this disease. Last of all, general metabolism in fever is considered in detail. The book on the whole provides interesting reading, although the personal pronoun is used a little more frequently than is necessary. J. A. C.

Gynecology of Obstetrics. By DAVID HADDEN, B. S., M. D. Cloth, $3.50 net. (*New York: The Macmillan Company, 1915.*)

There is nothing in this work which cannot be found much more compactly and accurately in the average text-book of gynecology. According to the author it is "an exposition of the pathologies bearing directly on parturition," but there is practically no reference to adnexal or uterine disease. The anatomy of the perineum and cervix, and the discussion of the various symptoms resulting from lacerations and their relief by operative treatment, occupy most of the 187 pages. The subject matter is quite commonplace and there is nothing new that is of scientific interest. There are many inaccurate statements that still further detract from its value. The author has attempted to explain the greatest variety of conditions as being due to perineal and cervical injuries and this attempt has led to many statements that are, to say the least, questionable.

Many of the illustrations are reproductions of micro-photographs and these are excellent. The colored photographs of the dissections of the pelvis are nicely executed, but are not to be compared with the usual semi-diagrammatic representations of anatomical material. E. D. P.

Therapie der Haut- und venerischen Krankheiten. By PROF. DR. J. SCHÄFFER. Cloth. Price 10 marks. (*Berlin: Urban & Schwarzenberg, 1915.*)

The chief value of this small volume lies in the first part, which deals with the general principles of therapy. Here the author takes up many of the seemingly small things, such as the way in which to apply medicaments, the cleansing of the skin before and after local applications, etc., which are so very important in treatment and which are most frequently not sufficiently emphasized in larger texts.

An attempt to arrange drugs in scales according to the intensity of their various activities is more didactic than practical, but will serve as a working basis for the student.

The part dealing with special therapy has nothing to recommend it above many other books of this character; and the fact that so many of the drugs advised are of a proprietary nature, and are expensive and difficult to obtain in America, renders the book, from the standpoint of prescriptions, of less use to the practitioner than one published in our own country. L. W. K.

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